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Ca

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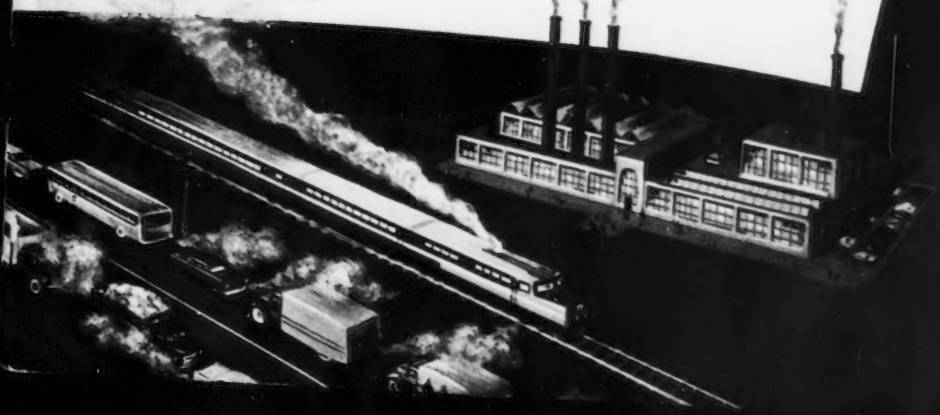
Cancer Progress

SMOKING AND HEALTH

It is my duty to warn all cigarette smokers that there is now conclusive evidence that they are running a greater risk of contracting cancer than non-smokers. The risk mounts with the number of cigarettes smoked. Giving up smoking reduces the risk.

MEDICAL OFFICER OF HEALTH

THE CENTRAL COUNCIL FOR HEALTH EDUCATION, TAVISTOCK HOUSE, TAVISTOCK SQUARE, LONDON W.C.1



When military defeat is inevitable the commander orders a "delaying action," never decisive or victorious, to cover a "withdrawal"—euphemism for retreat and defeat.

Dr. Little, Scientific Director of the Tobacco Industry Research Committee, is executing an ordered delaying action in the cigarette-lung cancer "controversy," which he refers to as a "battle."

This tactical maneuver, which is apparently agreeable to the other members of his Scientific Advisory Board, is to deny repeatedly the validity of the many authoritative reports indicating by accepted epidemiological, experimental, and pathological studies that cigarette smoking causes lung cancer; to prevent or delay, and to neutralize in this country any widespread public education, like that now being promoted in England, that would hurt sales of cigarettes; to mislead the public into believing that no change in smoking habits is indicated from the existing statistical and pathological evidence, nor will be until "direct experimental evidence" is at hand; and to convince the trusting, tobacco-consuming public of the industry's eleemosynary, "lasting interest in people's health."

With human lives at stake, smoking cannot be considered as innocent until proved guilty, but must stand guilty, on the evidence until proved innocent.

Presumably, the Chairman, his Board, and their sponsors would engage the medical profession and the public in "calm deliberation" for the next forty or fifty years, when such "direct evidence" could be available from a human guinea-pig experiment set up today. As a scientist he knows such a "direct-evidence" experiment is impossible, and he utilizes its impossibility for continuing productive, long-term delay. Success of this strategy is reflected in the continued increase in cigarette sales—an indication of the public's need for the facts. It will be interesting to follow the tobacco industry's response to the invitation of the Federal Trade Commission to cooperate in developing uniform specifications for testing cigarette smoke for tars and nicotine "to end confusion arising from widely varying tests conducted privately by the companies."

Most scientists closest to the total evidence now agree that cigarette smoking is a highly significant cause in the majority of cases of lung cancer.

The immediate duty of the physician, of the educator, of the parent, and of the governmental and voluntary health agencies is obvious—a concerted educational attack that will rout the formidable force executing the DELAYING ACTION and speed its spokesman on his prophesied, inevitable, penitential "TRIP TO CANOSSA."

Cover—Causes of Lung Cancer

This poster is one of several distributed through local authorities and voluntary organizations by The Central Council for Health Education, Tavistock Square, London, W. C. 1, England. Dr. John Burton, Medical Director of the Council, in transmitting this and other fliers, illustrations, speakers' notes, etc., writes that the Council is attempting to establish in the public mind the connection between smoking and cancer, without creating anxiety, which might lead to failure to report symptoms. He states that people do not stop smoking because they are frightened of cancer but because of various reasons which amount to an intellectual appreciation that it is a silly habit. The Council is trying to find out what it is about smoking that is so peculiarly satisfying to some people, when and why people start, and why and how some stop smoking.

NEWSLETTER

MARCH-APRIL, 1958

Recent results of the intriguing work by Scott and others (U. of Calif.) once again have drawn attention to the little understood role of iodine metabolism and thyroid function in carcinogenesis.

To recapitulate: Scott and co-workers several years ago injected I^{131} into rats shortly after transplanting tumors to them. In tumor-resistant animals, the iodine concentrated in the thyroid or was excreted, even during several days when the tumor grew vigorously before withering away. In susceptible animals, however, relatively little of the I^{131} went to the thyroid -- it concentrated largely in tissues around the tumor and in the skin, digestive tract, and plasma, and little was excreted. The same "iodide-trapping" phenomenon was observed in animals bearing spontaneous and induced tumors. Something in the tumor had perverted iodine metabolism.

That something, it turned out, was a large polypeptide. When injected into normal animals, the polypeptide promptly diverted iodine from the thyroid to wide areas of the body.

Now the Scott group have found out how it's done. The polypeptide somehow brings about the rupture of certain normal cells, especially mast cells which then empty their contents into their environment. Among the contents of mast cells are histamine (a metabolite of histidine) and 5HT (5-hydroxytryptamine or serotonin). Both of these compounds are required for anaphylaxis and other metabolic responses. In this instance, however, a tumor-abetting action may lie in their propensity for increasing capillary permeability -- a mechanism for diverting a glutton's share of blood-borne nutrient to the tumor. Whether this also enables the tumor to invade and metastasize is speculative. Whether heparin (another mast-cell substance) also aids the tumor is not known. Some investigators have reported increased clotting time in advanced cancer.

Now Scott and co-workers are giving susceptible animals the iodide-trapping polypeptide for two days before implanting tumors. The result: Tumor take and tumor size are significantly lowered. The possible mechanism: De-

pletion of mast-cell 5HT (which is excreted as 5Hindoleacetic acid) and frustration of the tumor's polypeptide. Therapeutic potential is limited by the fact that while prophylactic polypeptide discourages the growth of small transplants, it appears to enhance the growth of established tumors.

Scott's research impels a review of other evidence tending to relate the thyroid to tumor growth.

The thyroid hormones (one can only guess at this time that there may be as many as 10 or 20 active natural analogues of thyroxine) regulate oxidative metabolism, promote differentiation (or maturation, as in tadpoles) and uncouple phosphorylation. All these are regarded as essential problems in carcinogenesis. It now appears that some of the analogues may be more or less specialists. The well-known connective-tissue changes in myxedema constitute presumptive evidence that thyroid may maintain the integrity of tissues against invasive and metastatic cancer.

Tumor Induction and Suppression: Thyroid blocking (with thiouracil) increases and desiccated thyroid decreases tumors of ovaries transplanted to the mouse spleen (Gardner and Miller, Yale) . . . Thiourea protects rat liver against AAF-induced hepatoma but promotes thyroid tumors (Paschkis and Cantarow, Jefferson) . . . Highly invasive spontaneous thyroid tumors of Mexican swordtail fish regress under thyroxine, while thiourea elicits growth of thyroid tumors in ordinarily non-tumorous fish (Berg, Gordon, and Gorbman, Columbia) . . . Malignant tumors of the face develop in rats under prolonged treatment with thiourea (Rosin and Rachmilewitz, Hebrew University) . . . Hypophyseal adenomas were induced in mice with thyroidectomizing doses of I^{131} . . . Thyroid destruction in cancer-resistant rats brought mammary tumors to 40 per cent within 350 days; myxedematous patients had nine times, and thyroidectomized patients 14 times, the incidence of breast cancer found among hyperthyroid women (Rawson, SKI, quoting Hamilton and Lerman) . . . Thyroid atrophy (cause or effect) was found at autopsy in 59 per cent and other thyroid disease in an additional 27 per cent of women dead of breast cancer; thyroid disease was found at autopsy twice as often among prostatic cancer victims as among non-cancerous controls; and hyperplasia of adrenal and ovarian cortices (possibly due to hypofunctional thyroids) were observed with high fre-

(Continued after page 72)

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TOPIC: CAUSES OF LUNG CANCER

Address all correspondence to
WILLIAM H. STONER, M.D., *Editor*
American Cancer Society, Inc.
521 West 57 St., New York 19, N. Y.

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a glance . . .

one-minute abstracts of the current literature on lung cancer etiology . . .

Tobacco and Lung Cancer

The tobacco–cancer problem cannot be solved by ignoring its existence or depreciating its importance. Work already completed and investigations now in progress indicate that the problem will be solved. Proof that smoking is the cause of cancer in man is entirely statistical and epidemiological, but substances carcinogenic in animals have been isolated from cigarette-smoke tars. When an agent is found to be carcinogenic to a variety of animals, and human epidemiological data are not inconsistent with this finding, the burden of proof rests upon those who claim that the agent is not carcinogenic to man. The public is unable to evaluate the present facts, in part because of the confusion that special interests in some countries have added to the situation. Public health services of different countries are evaluating the data at hand and must decide whether lives are more important than economic considerations. All the physician can do is to present the facts to the public; and the facts are these: Some 80 per cent of all lung cancers occurring in males today would not have occurred but for tobacco smoking. About 10 per cent of males more than 25 years of age who smoke in excess of 20 cigarettes a day will develop lung cancer by the age of 75. A person smoking 40 cigarettes a day is 70 times as likely to develop lung cancer as is a nonsmoker. The hazard is proportional to the amount of smoking. Lung cancer could be largely prevented by abolishing the use of tobacco; but because of the economic factors involved and of firmly entrenched habits such advice will not be heeded, regardless of how strong the evidence is. Accordingly the author is pursuing investigations leading to reduction of the carcinogens in tobacco and its products. The waxes covering the tobacco leaf contain most of the aliphatic hydrocarbons which burn to carcinogens. Removal of these waxes, together with effective filtration of cigarette smoke (which is not yet commercially available), and, above all, moderation of smoking habits would minimize the hazards pending the advent of a more effective solution.

Wynder, E. L.: Towards a solution of the tobacco-cancer problem. Brit. M. J. 1:1-3, Jan. 5, 1957.

The "Moderation" Myth

In England at least 80 per cent of the incidence of cancer of the lung in men is associated with smoking. In New Zealand, where more tobacco is smoked, the incidence is about 50 per cent lower, suggesting that a substantial, but lesser, part of

the risk associated with smoking in England is determined by the coincident influences of smoking and urban life, probably air pollution. The elimination of smoking or of the effects of urban life could lead to a major reduction in mortality. It is unfortunate that the association of one should have been used to discredit the value of prophylaxis in the other. However, there is a risk associated with smoking which is independent of place of domicile. In tuberculosis, smoking is related to more than 50 per cent of cases in men more than 30 years of age and to about 25 per cent in women. Most cases of bronchitis would not occur in the absence of smoking. The myth of moderation in smoking as a remedy of its evil effects is exploded by a detailed mathematical analysis (methods described) of the Doll and Hill data on smoking and lung cancer, of Lowe on pulmonary tuberculosis, and of Leese on chronic bronchitis. This analysis shows that exhortations directed exclusively toward moderation in smoking may have paradoxical consequences. There is no threshold. The relation of degree of smoking to liability to both cancer and tuberculosis is such that the harm done *per cigarette per day* decreases with increasing amounts smoked. The incidence of cancer and of tuberculosis would be lower if half of all smokers stopped smoking than if all smokers halved their smoking. Damage within any age group would be at a maximum if distribution of smoking were even. If sales of cigarettes were maintained at a fixed level or rate of increase by advertising, the discouragement of heavy smoking would increase the incidence of lung cancer and tuberculosis. The "common sense" view of many smokers, clinicians, and tobacco companies is that moderation is fairly innocuous, and that only the heavy smoker is exposed to an appreciable risk. This type of response is true of alcohol, but the analogy for tobacco is false. In drinking, the pleasure and the damage are caused by the same substance, and irreversible damage follows only repeated exposures to concentrations in excess of those usually demanded for pleasure. On the other hand, in tobacco smoke the constituents responsible for pleasure are probably different from those responsible for damage, and there is no *a priori* reason why amounts of tobacco usually regarded as insufficient to confer pleasure should be inadequate to cause disease. Nor is there any reason to suppose that by some coincidence the factors conferring pleasure and disease should be so proportional that moderation in indulgence should give freedom from illness. The curtailment of life due to the common respiratory diseases in men in England and Wales is more than 1,200 man-years *daily*. Probably well over one-half of this loss of life is related to smoking.

Edwards, J. A.: Contribution of cigarette smoking to respiratory disease. Brit. J. Prev. & Social Med. 11:10-21, Jan., 1957.

Etiology and Prevention of Lung Cancer

Twenty retrospective studies of patients with and without lung cancer in seven countries have all led to similar conclusions concerning the association of this disease with smoking. The evidence is further strengthened by prospective studies. The death rate for lung cancer is low in nonsmokers and increases steadily with the amount smoked till it is more than 20 times higher among heavy smokers. The simplest explanation of the known facts is that cigarette smoking is a major cause of lung cancer. Detailed pathological studies of the bronchial mucosa of patients dying of various types of cancer show that hyperplasia and metaplasia of the basal-cell layer and the presence of carcinoma in situ is progressively more common as the amount smoked increases, and is commonest of all among patients who have died of lung cancer. The difference in mortality in different countries correlates well with the consumption of cigarettes in those countries 20 years earlier. The rates among men and women correspond with their past smoking habits. Tobacco tar is capable of producing skin cancer in animals. This does not prove that tobacco causes lung cancer in man,

but it provides a method whereby the carcinogenic agent may be isolated. The five carcinogens found in tobacco smoke provide a rational explanation for the human observations. R. W. Raven, in discussion, stated that, with the statistical and laboratory data now available, there is a wonderful opportunity to combat one of the most fatal varieties of cancer. It is not enough to inform the public of the dangers to health and life from smoking tobacco; they must be told what action to take to avoid or to minimize these dangers. In many people smoking is an addiction and doctors must be prepared to help during the weaning period. Mr. Raven reviewed the recent study of smoking in schools in England by the Marie Curie Memorial Foundation. Among boys the percentage of regular smokers is increasing. Precocious smoking is more common among groups of lower intelligence. Parents often permit or condone the habit. Parents, teachers, ministers of religion, and other adults must give example. Attention should be given to protection of people spending various periods in confined spaces heavily polluted with products of tobacco combustion—in halls, cinemas, and transports. R. B. D. Stocker, in discussion, proposed that lung cancer prevention requires scientific study of the causation and prevention of the smoking habit, particularly the nature of nicotine addiction. In coffee the same constituent, caffeine, is responsible for both the good and bad effects. In tobacco the carcinogens and their precursors are separate entities from the pleasurable, habit-forming nicotine. W. C. Turner, emphasizing the role of atmospheric pollution, asserted that the amount of extraneous carbonaceous matter found in the lung at postmortem is sufficient to differentiate the town-dweller from the countryman. Dr. Doll, in closing, stated that there are causes of lung cancer other than smoking—atmospheric pollution, specific industrial factors, and possibly naturally occurring radioactivity and residual scarring from chronic pulmonary infection.

Doll, R.: Lung cancer and smoking. Roy. Soc. Promot. Health J. 77:247-250; disc. 250-254, June, 1957.

From the Horse's Mouth

Statistical study of some 70,000 plant employees of the American Tobacco Company showed that more of them smoke cigarettes (including the free pack a day) than the general population of the United States as follows: white males 77.2:49.9 per cent, white females 44.4:23.6 per cent, nonwhite males 84.1:48.4 per cent, and nonwhite females 61.7:22.9 per cent. Per capita cigarette consumption was higher, and there were twice as many more-than-a-pack-a-day smokers among the employees as in the general population. Despite this increased cigarette consumption this providentially favored group showed increased longevity, lower death rates from cancer in general and from cardiovascular diseases including coronary disease, and a death rate from respiratory cancer no higher, than those of the general population. According to the authors, these findings have "added significance from the fact that no sampling error is involved in the methodology" as in previous studies. Rigdon (Univ. of Texas) in discussion stated that scientists who support the statistical association between cigarette smoking and higher overall death rate, higher death rate from lung cancer, and higher death rate from cardiovascular diseases will find this study very difficult to refute. [See next abstract. —ED.]

Haag, H. B., and Hanmer, H. R.: Smoking habits and mortality among workers in cigarette factories. Indust. Med. 26:559-562; disc. 562, Dec., 1957.

Sampling Errors Exposed

The conclusions of the report abstracted above have added significance from the fact that they will be used irresponsibly "with respect both to the influencing of personal habits and to the pursuit of wealth." Haag and Hanmer assume that their tobacco employees differ from the general population only in their smoking habits, and in age, sex, and color distribution for which allowance can be made by proper choice of specific death rates. But they have not considered how their employees are selected, how rapid is the labor

turnover, what the sex, age, and color distributions are, how long the employees have been with the company, or how many employees leave for reasons other than retirement. Medical screening of a sub-population invalidates any conclusions from comparison with the general population; the screened sub-population is not then a representative sample of the general population. Such a sampling bias is particularly important in a short (four years) survey dealing with chronic diseases, and with a high labor turnover, including employees with early signs of chronic disease seeking more suitable employment. Applying the conventional test for significance to the 4 deaths from lung cancer, it is shown that the investigation could not have discriminated between an observed value of 0 and 8; 7 is the number calculated from the hypothesis of Hammond and Horn. It is concluded (1) that the evidence advanced does not warrant the claim that "no sampling error is involved in the methodology," and (2) that the conclusions of Haag and Hanmer should not be used as a guide to human behavior.

Case, R. A. M.: Smoking habits and mortality among workers in cigarette factories. Nature 181:84-86, Jan. 11, 1958.

Tobacco, Autos, and Lung Cancer

In order to assess the relative importance of cigarette smoke, motor exhaust fumes, and general urban air pollution in the incidence of lung cancer, survey was made, in and around Cincinnati, of the smoking habits of men and women, their annual driving mileage, and the distribution of lung cancer deaths. Tobacco smoking was found to be significantly related to lung cancer incidence with or without additional heavy exposure to urban motor traffic or general air pollution. Annual driving mileages of more than 12,000 a year also were found to be related significantly to lung cancer incidence among urban men but not among those who were heavy smokers. Deaths from lung cancer were significantly more frequent among men living in the Basin district, where air pollution is greatest and natural ventilation poorest, than among those living in suburban areas. Lung cancer rates in men, urban or rural, who did not smoke did not differ significantly from the low rates among the women of all groups. It is concluded that the alarming rise in the incidence of lung cancer is predominantly a hazard of urban tobacco smoking—a hazard intensified by heavy exposure to urban traffic. Thus, it is seen that, of two of the etiologic factors—cigarette smoking and air pollution—cigarette smoking is by far the more closely related to the incidence of lung cancer.

Mills, C. A., and Porter, M. M.: Tobacco smoking, motor exhaust fumes, and general air pollution in relation to lung cancer incidence. Cancer Res. 17:981-990, Nov., 1957.

THE GRAND STRATEGY

Like a championship chess game, the bronchopulmonary-cancer "controversy" develops in a series of moves and countermoves made before a passive and confused public. . . . The tobacco interests have shown themselves assertive and aggressive. . . . Their gambit is to iterate and reiterate that whereas smoking may be a factor no one has yet proved that it may be an unassisted cause of cancer. . . . The grand strategy of the tobacco industry is becoming abundantly clear—smoking may be a factor but not a cause and statistics do not constitute proof—[and] should ensure a casuistic stalemate for many years. . . . With this defense the game can never be lost, if success is to be judged by advertising copy and not by human lives. Most consumers are in no position to decide the facts. They need to hear the dispassionate opinion of experts, an opinion that is allowed to express itself objectively and without immediate countermoves by those who have incentives other than that of reaching the correct decision.

—Editorial: New England Journal of Medicine 258:99, Jan. 9, 1958.

Lung Cancer Death Rates in Relation to Smoking*

With the assistance of over 20,000 volunteer workers of the American Cancer Society, information was obtained on the smoking habits of 187,783 white men, aged 50 to 69, who were then followed for 44 months. A high degree of association was found between total death rates and cigarette smoking; a far lower degree of association between total death rates and cigar smoking; and a small degree of association between total death rates and pipe smoking.

There being a considerable relationship between cigarette smoking and total death rates, the next step was to determine which diseases were involved. The available source of information was cause of death as recorded on death certificates supplemented by more detailed medical information where cancer was mentioned.

An analysis of the data showed the following relationships with cigarette smoking: 1) an extremely high association for a few diseases such as cancer of the lung, cancer of the larynx, cancer of the esophagus, and gastric ulcer; 2) a very high association for a few diseases such as pneumonia and influenza, duodenal ulcer, aortic aneurysm, and cancer of the bladder; 3) a high association for a number of diseases such as coronary artery disease, cirrhosis of the liver, and cancer of several sites; 4) a moderate association for cerebral vascular lesions; 5) little or no association between cigarette smoking and a number of diseases including: chronic rheumatic fever, hypertensive heart disease, other hypertensive diseases, nephritis and nephrosis, diabetes, leukemia, cancer of the rectum, cancer of the colon, and cancer of the brain; 6) a lower death rate among men who had given up cigarette smoking for a year or more before being enrolled in the study than among those who were smoking cigarettes regularly at that time.

The findings in relation to lung cancer may be summarized as follows:

Of a total of 11,870 deaths reported, 448 were attributed to lung cancer. These showed a high degree of association with cigarette smoking. Of these 448 deaths, 32 were from adenocarcinoma and 295 cases were microscopically proved with good evidence of being primary bronchogenic carcinoma. For this group of 295 well established cases the association with smoking habits was even more pronounced than for the total group. This is shown in Fig. 1 together with the number of deaths, the number of men at start, and the age-standardized death rate per 100,000 per year by type of smoking history. (Men who smoked both pipe and cigarettes are not shown.)

Fig. 2 shows that the death rate (well established cases) goes up sharply with the amount of cigarette smoking for men with histories of regular smoking of cigarettes only. The age-standardized death rate for the men with this diagnosis, smoking two or more packs a day, was 217.3 per 100,000 per year. In contrast, the age-standardized death rate from microscopically proved cancer of all sites combined was only 177.4 per 100,000 per year for men who never smoked. The death rate from bronchogenic carcinoma alone among two-pack-a-day cigarette smokers was higher than the total cancer death rate of men who never smoked!

Lung cancer death rates of men who stopped smoking are shown in Fig. 3. Men currently smoking one pack or more of cigarettes a day in 1952 had a death rate from well established lung cancer of 157.1 per 100,000 per year. Those who previously smoked at this level but had stopped smoking for from one to ten years had a rate of 77.6, and those who

*Abstracted from Hammond, E. C., and Horn, D.: Smoking in relation to death rates. J.A.M.A. In press. Read at the 106th Annual Meeting of the American Medical Association, New York City, June 4, 1957.

had stopped for ten years or longer had a rate of only 60.5.

The death rate from well established lung cancer exclusive of adenocarcinoma was found to be higher in cities than in the country. The age-standardized death rate was 34 per 100,000 in rural areas and 56 in cities of over 50,000 population—39 per cent lower in the rural areas. Cigarette smoking is more common in cities than in the country. Standardized for smoking habits as well as for age, the rate was 39 in rural areas and 52 in cities of more than 50,000 population—still a 25 per cent difference. This difference may be caused by some etiological factor associated with city life, or to better case finding and diagnosis in the cities. However, the lung cancer death rate was low among men who never smoked cigarettes regularly and high among cigarette smokers in large cities, small cities, suburbs, towns, and rural areas. Whatever the urban factor may be, its effect on lung cancer death rates is small compared with the effects of cigarettes as shown in Fig. 4.

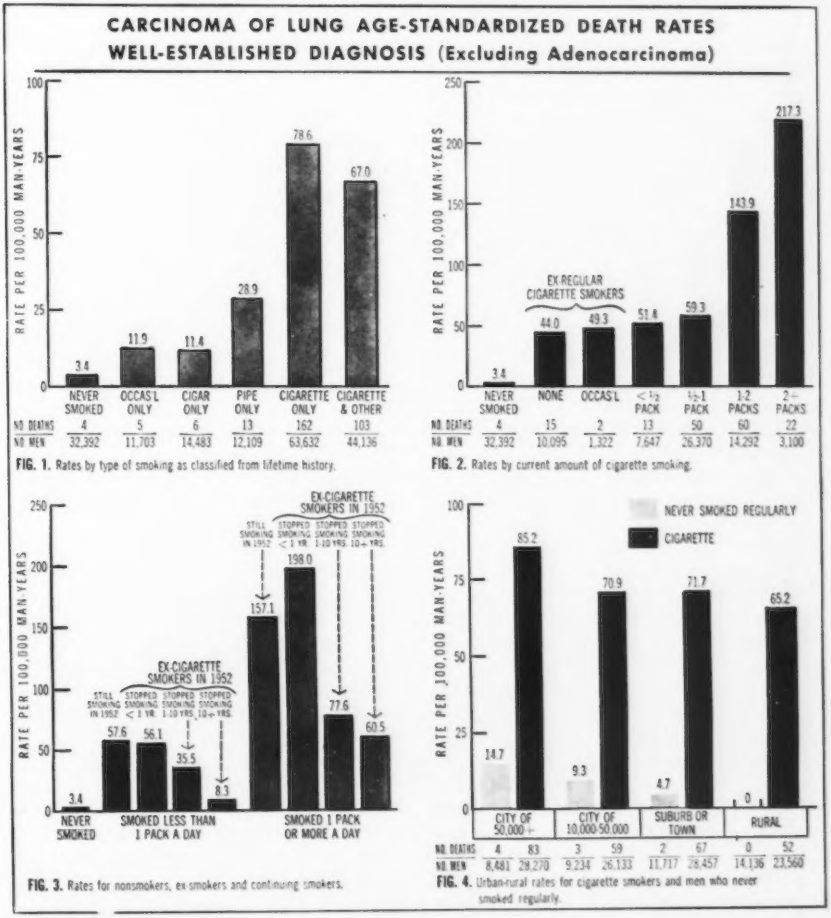

FIG. 1. Rates by type of smoking as classified from lifetime history.

FIG. 2. Rates by current amount of cigarette smoking.

FIG. 3. Rates for nonsmokers, ex-smokers and continuing smokers.

FIG. 4. Urban-rural rates for cigarette smokers and men who never smoked regularly.

Lung Cancer and Excessive Cigarette Smoking

Statement By Surgeon General Leroy E. Burney of the Public Health Service, Department of Health, Education, and Welfare, July 12, 1957.

The Public Health Service is, of course, concerned with broad factors which substantially affect the health of the American people. The Service also has a responsibility to bring health facts to the attention of the health professions and the public.

In June, 1956, units of the Public Health Service joined with two private voluntary health organizations to establish a scientific Study Group to appraise the available data on smoking and health. We have now reviewed the report of this Study Group and other recent data, including the report of Dr. E. C. Hammond and Dr. Daniel Horn on June 4th to the American Medical Association in New York.

In the light of these studies, it is clear that there is an increasing and consistent body of evidence that excessive cigarette smoking is one of the causative factors in lung cancer.

The Study Group, appraising 18 independent studies, reported that lung cancer occurs much more frequently among cigarette smokers than among non-smokers, and there is a direct relationship between the incidence of lung cancer and the amount smoked. This finding was reinforced by the more recent report to the AMA by Drs. Hammond and Horn.

Many independent studies thus have confirmed beyond reasonable doubt that there is a high degree of statistical association between lung cancer and heavy and prolonged cigarette smoking.

Such evidence, of course, is largely epidemiological in nature. It should be noted, however, that many important public health advances in the past have been developed upon the basis of statistical or epidemiological information. The Study Group also reported that in laboratory studies on animals at least five independent investigators have produced malignancies by tobacco smoke condensates. It also reported that biological changes similar to those which take place in the genesis of cancer have been observed in the lungs of heavy smokers. Thus, some laboratory and biological data provide contributory evidence to support the concept that excessive smoking is one of the causative factors in the increasing incidence of lung cancer.

At the same time, it is clear that heavy and prolonged cigarette smoking is not the only cause of lung cancer. Lung cancer occurs among non-smokers, and the incidence of lung cancer among various population groups does not always coincide with the amount of cigarette smoking.

The precise nature of the factors in heavy and prolonged cigarette smoking which can cause lung cancer is not known. The Public Health Service supports the recommendation of the Study Group that more research is needed to identify, isolate and try to eliminate the factors in excessive cigarette smoking which can cause cancer.

The Service also supports the recommendation that more research is needed into the role of air pollution and other factors which may also be causes of lung cancer in man.

To help disseminate the facts, the Public Health Service is sending copies of this statement, the Study Group report and the report of Drs. Hammond and Horn to State Health Officers and to the American Medical Association with the request that they consider distributing copies to local health officers, medical societies and other health groups.

While there are naturally differences of opinion in interpreting the data on lung cancer and cigarette smoking, the Public Health Service feels the weight of the evidence is increasingly pointing in one direction: that excessive smoking is one of the causative factors in lung cancer.

Dr. Little's Reply

Statement of July 12, 1957

The statement issued today by the Surgeon General adds nothing new to what has been known about the cause of lung cancer. It reflects the opinions of some statisticians and the relatively few experimental scientists who have actively charged that cigarette smoking is a cause of lung cancer.

No new evidence has been produced since the Scientific Advisory Board of the Tobacco Industry Research Committee last stated its position on this question on May 1, 1957. At that time, I said that, although anyone has the right to state an opinion on cancer causation, "the Scientific Advisory Board questions the existence of sufficient definitive evidence to establish a simple cause-and-effect explanation of the complex problem of lung cancer."

This is most definitely our position today.

The Surgeon General's own statement makes clear that "lung cancer occurs among nonsmokers and the incidence of lung cancer among various population groups does not always coincide with the amount of cigarette smoking."

The Public Health Service also supports the recommendation that more research is needed into the role of air pollution and other factors.

For the past three years, the Scientific Advisory Board has had the matter of tobacco use and human health under continuous review and consideration, both in the Board's regular meetings and in individual endeavors. We have had the responsibility of guiding a research program through which the Tobacco Industry Research Committee already has provided 2.2 million dollars for grants to independent scientists working in the fields of cancer and other challengers of human survival.

This research, thus far, has produced no evidence that cigarette smoking or other tobacco use contributes to the origin of lung cancer.

Many experiments on inhalation of cigarette smoke in animals have failed to produce a single cancer similar to the most prevalent type of lung cancer in humans. This and other facts show the need for continued unbiased research into the cause of cancer and other diseases.

Statisticians have so far failed to consider adequately many variables in human habits, environments and constitution, such as biological susceptibility to cancer, the effects of previous lung disease, hormonal influences and many other factors. It should be remembered that statistical association does not prove cause and effect.

In advising and educating the public, the Scientific Advisory Board believes that one should be as cautious in accepting a claim that a cause has been found for cancer as they have found it wise to be in the past accepting a claim of a cure for cancer.

The Scientific Advisory Board intends to continue expansion of its program of making grants-in-aid to qualified scientists who propose to explore those areas of human health where the basic research problems appear most compelling and the prospect of results appears to be most promising.

". . . lucri bonus odor . . . "

". . . the sweet smell of gain makes the smell of tobacco less perceptible and less offensive. . . ."

—Ramazzini, B.: De Morbis Artificum. Modena. 1700. [Translation by Wright, W. C.: University of Chicago Press. 1940; p. 147.]

An Open Letter to Dr. Clarence Cook Little

David D. Rutstein, M.D.

Dear Dr. Little:

As a professor of preventive medicine, I have been deeply concerned, as I know you have, by the constantly increasing death rate from lung cancer in the United States and in other parts of the world. Over 25,000 people in the United States die from lung cancer each year, and the number is increasing by about 2000 every year. This disease now kills more men than any other form of cancer.

What is the evidence that cigarette smoking is responsible for most of this increase? Eighteen studies in five countries show either that patients with lung cancer are predominantly cigarette smokers, or that cigarette smokers have more lung cancer than do nonsmokers. All but one of these eighteen studies show that the more and the longer you smoke cigarettes (but not pipes and cigars), the more likely you are to get lung cancer. Depending on the amount and duration of the smoking, the rate of occurrence of lung cancer is from five to thirty-five times greater among cigarette smokers than among nonsmokers. Most important, in all of the medical literature there is not one study which shows no relationship between cigarette smoking and lung cancer. These results, it seems to me, are more than just "the opinion of a few statisticians," as you stated on last July 12.

There is another kind of evidence which links cigarette smoking to the development of lung cancer. Examination of the lungs of cigarette smokers under the microscope reveals precancerous changes. The extent of these abnormalities is directly proportional to the amount and duration of cigarette smoking.

These changes were least common in the lungs of those who did not smoke cigarettes regularly and most common in the lungs of those dying of lung cancer.

Reprinted from The Atlantic 200:*41-43, Oct., 1957.*

There is a third but very weak kind of evidence which should be mentioned for completeness. Substances have been found in cigarette smoke which are similar in their chemical structure to compounds which produce cancer in animals. Actually, a few investigators have been able to produce cancerous changes following application of such substances to the skin of mice. As a cancer research worker of many years experience, you know that evidence obtained on animals cannot be translated directly to man. You know that conclusive evidence on human lung cancer has to be obtained from observations on man. At present, therefore, these positive results in animal experiments add little to our understanding of human lung cancer.

You have consistently ignored or brushed off all of the human evidence whenever a statement relating cigarette smoking and lung cancer has been released to the press by a research worker, by the British government through its Medical Research Council, or by the Surgeon General of the United States Public Health Service speaking for the United States government. You have stated that there is nothing new, that the evidence is merely "statistical," and that no "cause and effect relationship has been demonstrated." Your statement troubles me because I had always thought that such evidence *is* valid; I had been taught to believe that it is essential for medical research workers to follow statistical principles in all their investigations. What is wrong with a statistical study? Do not statistical principles come into play whenever anything is counted in any scientific study, whether performed in the laboratory or in the field? Statistics are, after all, the rules by which things are counted, and it is impossible to do any experiment without counting up the results.

I don't know exactly what you mean by "cause." When you question the eighteen studies which show a relationship between cigarette smoking and lung cancer as being only "statistical," I think what you really mean is that these studies are not as well controlled as laboratory experiments. If we think about it, we realize that even in laboratory experiments, no matter how performed, the results are really nothing more than a statistical association between two events. The laboratory result becomes more valid if one can perform a series of experiments in sequence, because one can frequently rule out factors which may interfere with its interpretation.

On the other hand, in the study of epidemics of disease as they occur in a population, one can only observe what actually happens. This is as true for epidemics of influenza as it is for the present epidemic of lung cancer. This limitation does not deny the validity of the epidemiologic observation; it merely demands more care in interpretation. It requires analysis of the plan and results of each study and a comparison of the data of many studies planned along different lines. In the case of cigarette smoking and lung cancer, one may get some reassurance from the unanimity of results from the many different approaches that were used in the eighteen studies. It is unlikely that all would have been affected in exactly the same way by extraneous factors. Moreover, these results are confirmed by the increase in precancerous lesions in the lungs of smokers.

In spite of possible limitations of the method of study, the control of many human plagues in the past has depended solely on the kind of information which you have criticized as being only "statistical." This was certainly true before the discovery of bacteria by Pasteur about 1860. Let's look at the record and see how it applies to the present situation.

In 1796, when Jenner recommended vaccination with cowpox for protection against smallpox, he did not know the "cause" of smallpox. He knew only that milkmaids who previously had cowpox had immunity against smallpox. This was purely a statistical association. The virus of smallpox was not discovered until the early 1900s—over a century after the disease had been brought under control in civilized countries. Would you have recommended that vaccination against this highly fatal and widespread disease should have been delayed for a century because the evidence for it was only "statistical" and because Jenner had not discovered the "cause" of the disease?

Again, in 1854, during an epidemic of cholera in London, John Snow recognized the statistical association between cases of cholera and the drinking of water supplied by one of London's many water companies. John Snow inferred from his observations that a noxious substance causing cholera must have been transmitted by the particular water company, although the "cause" of cholera was not to be clearly defined for another forty years. Would you have said that the recommendations of John Snow were not to be applied in London because he did not know the "cause" of cholera? Perhaps one cannot apply the same rules to cigarettes as one does to germs. But the Southwark and Vauxhall Company, which pumped the sewage of the Thames through its private water supply, was probably disturbed by the charge that its water was responsible for the cholera epidemic.

Other diseases, such as rabies in Scandinavia, have also been controlled without information as to "cause." Unfortunately the opposite is also true. For example, typhoid fever in Devonshire could have been prevented if Dr. William Budd's epidemiological observations had not been ridiculed by the clinicians of his time.

Remember, Dr. Little, I am not recommending that people be forbidden to smoke cigarettes. Fortunately, our citizens can make their own decisions about matters such as these. But in a democracy, citizens have the right to be given the facts. They also must be protected by their government, as they were in a recent statement by the Surgeon General of the United States Public Health Service, against a smoke screen of irrelevant and confusing details.

In objecting to a public health program to diminish lung cancer by urging a decrease in cigarette smoking, you referred on July 12 to "variables in human habits, environmental and constitutional, such as biologic susceptibility to cancer, the effects of previous lung disease, hormonal influences and many other factors." These influences, as well as air pollution, are undoubtedly of some importance. But what do they have to do with the facts that the large majority of cases of lung cancer occur in cigarette smokers, that the longer and the more the individual smokes the more likely he is to have lung cancer, and that smokers have precancerous lesions in their lungs?

Actually, the evidence for the association between cigarette smoking and lung cancer is stronger than Jenner's evidence when he recommended vaccination against smallpox. This association is as strong as the basis for John Snow's recommendations for the control of cholera in London. Why do you insist that we find the "cause" of lung cancer before public health authorities be permitted to make any effort to control this disease?

I agree with you that further research must be carried on as intensively as possible so that we may completely control lung cancer and so that smokers can inhale their cigarettes in complete safety. At the same time, our citizens must be told clearly of the present risk of smoking any of the filtered or non-filtered cigarettes now available. But we must go even further. We must not limit our research on cigarette smoking to its relationship to lung cancer. As far back as 1938, Raymond Pearl of Johns Hopkins showed that non-smokers lived longer than smokers. Since that time, increasing evidence has been accumulating that other diseases, particularly coronary heart disease in young men, may be more common among cigarette smokers than among non-smokers. It will be important to confirm or deny such relationships because a small increase in a very common illness like coronary disease may cause many deaths. And the people must be allowed to know.

The Tobacco Industry Research Committee is to be complimented on the large sum it has allocated for research on the relationship of smoking to lung cancer. This enlightened approach seems inconsistent with the committee's policy of blind opposition to any attempt at public health control of lung cancer. Shouldn't this committee take a cue from the experience of the liquor industry after Prohibition and at least counsel moderation in smoking?

Although I realize that your committee does not perform research, with your leadership it could aid in setting up an experiment to answer the crucial question: Will a decrease in cigarette smoking result in a concomitant decrease in the death rate from lung cancer? I am optimistic enough to believe that a study could be set up to answer this question. Volunteers could be randomly divided into two groups—one being urged to stop and the other to continue cigarette smoking. There will probably be enough difference in the smoking habits of the two groups to measure possible differences in the death rate from lung cancer.

The results of such an experiment would provide the basis for a continued public health program. The laboratory research on the basic mechanism of the disease would, of course, meanwhile be carried on.

In the meantime, Dr. Little, is there really any justification for your continuing to demand the discovery of the "cause" of lung cancer before we attempt to save human lives by recommending a decrease in cigarette smoking? Lung cancer is a serious disease which causes much suffering and cuts down people in the prime of life. Should not public health authorities immediately recommend the obvious remedy suggested by sound epidemiologic observation and confirmatory laboratory evidence? If not, why not?

David D. Rutstein, M.D.

All that is necessary for the triumph of evil is that good men do nothing.
—Edmund Burke.

The Public and Smoking

Fear or Calm Deliberation?

Clarence Cook Little

We all agree, I am sure, that excess in and abuse of any human activity are undesirable and should be discouraged, whether it is the use of alcohol or coffee or tobacco, or the function of eating, of exercise or inactivity, of work or recreation. For the vast majority, however, the temperate expression of most of these same activities is an essential part of total health and well-being.

When any of these commonplace activities falls under suspicion as being a specific factor in the causation of human disease, we can agree also that this is a matter for serious consideration, but we must be extremely cautious in evaluating the basis for such suspicion and the extent of the supposed risk involved, and in avoiding the creation of fear and panic.

This is especially true today, when we are dealing with ailments, such as cancer and heart disease, of people mostly in advanced age groups. These do not, so far as our present knowledge goes, fit into the categories of the old-time pathologists—they are not specific diseases produced by specific causes with specific patterns of injury to specific tissues.

It is now generally agreed that they are, at least in part, diseases related in some way to present-day stress, modern environment, and to extension of life into the problem of old age. The worries of home, of business, of driving along highways, of crowded living, the search for relaxation and, not the least, the fears of being sick or of catastrophe have an untold effect upon the body and, if sufficiently intense, may certainly lead to illness, if not cause it.

As to seeking specific causes of cancer, and also heart disease, science is only now on the threshold of what I hope will be great advances in developing better methods of testing the biologic activity of many, many substances that we all use or are exposed to from day to day and, more important, of assigning to them their relative place in the scale of risks we assume in our daily lives. For it cannot be gainsaid that while there is an absoluteness about the hazards to life, there is no such thing as absolute safety for life. The very things that are essential or important to continued, effective living may be harmful or even fatal under conditions of misuse or abuse.

In the field of tobacco use and health, all concerned admit the need for more knowledge and research. Differences exist mainly over the evaluation of our present knowledge, or lack of it, and the direction and emphasis of future research.

There are some who feel and proclaim that "beyond reasonable doubt" cigarette smoke contains one or more as yet unknown substances that may cause cancer in man. They would concentrate their research on isolating, identifying, or "removing" these substances even though no such agent has been discovered experimentally.

Others believe, however, that the existence in tobacco smoke of substances carcinogenic to the lungs of men has not been and cannot be proved by statistical associations or by painting the skin of mice of certain specific strains with highly concentrated extracts of tobacco smoke. They therefore focus attention on development of more exact and more direct methods of assaying the cancer-inducing powers of suspected substances. In this direction may be found contributions not only to the smoking question but also to the total problem of bio-assay of other substances.

Fear or Calm Deliberation?

Generally speaking, the public believes in dicta from scientists or public health groups. Doubt, suspicion, fear, and mental tension can be created and maintained by

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one type of presentation of a situation. Balance, poise, a judicial attitude, and calm deliberation can be engendered by another. For at least four years there have been repeated, sensational, and fear-arousing statements and resultant headlines on the theoretical lethal nature of tobacco smoke.

The repeated expression of these views, however, is no measure of their general acceptance by all who are concerned with the problems involved. For instance, the statistical evidence in support of the cigarette theory has not been accepted as proof of generalized conclusions about smoking by a number of distinguished statisticians, among whom may be mentioned especially Dr. Joseph Berkson, Section of Biometry and Medical Statistics of the Mayo Foundation for Medical Education and Research in Rochester, Minnesota.

There are certain unfeatured but fundamental contradictions in different statistical papers from which points of agreement have been selected for presentation by advocates of the "cigarette guilt" theory.

For example, the implication of the American school of cigarette theorists is that inhalation and, therefore, direct contact of smoke with lung tissue is an important factor in the origin of lung cancer. On the other hand, certain British investigators state that it would appear that inhalation is a "negligible" factor. If this is the case, direct contact is not an important element. In any attempt to identify a suspected agent or agents, these two possibilities are an unsolved complication and are evidence of incomplete knowledge.

The clinical pathological data of one American Cancer Society grantee was hailed by the then medical director of that society as "the very evidence skeptics demanded." These same data have not been so evaluated by a considerable number of trained clinical pathologists not affiliated with the American Cancer Society but familiar with much more data of a similar nature.

The reports of inducing skin cancer on some mice by smearing highly concentrated tobacco smoke condensates have been countered not only by similar experiments failing to result in cancer but by universally negative carcinogenic results reported by a number of investigators following the inhalation of cigarette smoke or its injection directly into the lungs of rodents.

Such contradictions in findings and interpretations could be continued at length, and indeed have been in many authoritative scientific publications, but these few are cited merely as evidence that the status of research into lung cancer involves many unresolved differences in concepts about possible causation and also about its relative incidence and increased frequency.

In accepting and carrying out the responsibility of developing a research program in tobacco use and health for the Tobacco Industry Research Committee, my colleagues on the Scientific Advisory Board and I believe the cause of scientific investigation is best served by adherence to our stated position that definitive conclusions or predictions of individual risks are unwarranted by the present state of knowledge in this complex field.

Industry Assures Freedom in Research

Some people question, as might be expected, whether the tobacco industry is honest in its efforts to find the whole truth. The conditions under which Tobacco Industry Research Committee grants are made guarantee complete freedom, unhampered conduct of research, and uncensored publication of any and all results.

The tobacco industry was and is aware of the seriousness of the implications in the charges against smoking. The industry intends to support research until these charges can be proved or disproved by direct experimental evidence. Even cynics will admit that the industry cannot afford as a practical business matter to offer products which have been so definitely attacked without making every effort to find out the whole truth and, if and when any substance is identified and is shown to be harmful, to do its best to eliminate it.

The industry is aiding research for scientific facts and will continue to do so. But it need not accept as final opinions based on incomplete evidence that is challenged by others. Nor does it feel able to "remove" from its products substances the nature, presence, and existence of which are generally admitted to be unknown.

In these circumstances, the industry chose a course that is unusual, if not unique, for business-supported research. Scientists were given full responsibility for determining what research is needed and who should do it. The Scientific Advisory Board, of which I am chairman, has complete freedom in allocating the research monies, now amounting to some $2.2 million, to investigators in leading U. S. research, medical, and educational institutions. The board considers proposals for projects on their scientific merits and the prospects of constructive findings. The board may also initiate research ideas and then seek out qualified scientists to develop and conduct the needed lines of investigation.

It is important for the public to remember that the members of the Scientific Advisory Board, in their approach to this research responsibility, take the position that smoking has not been proved guilty or guiltless in matters affecting human health. Their attitude is that statistical and indirect evidence does not prove its guilt as a causative agent. The open question of its innocence or its guilt can best be answered through unhampered research for the full facts.

The Right to Learn and to Inform

The board members do not deny the right of any individual to state his belief in the guilt of smoking. Along with many independent research scientists, they do and will as scientists insist on maintaining their right to their own criteria for judgment and for the opportunty to inform the public concerning the reasons for their position.

They will do this until they possess evidence which they consider meaningful and conclusive on each and every research step. They will do this in spite of expensive and extensive pressure propaganda, and in spite of personal misinterpretations and attacks.

These statements of honest doubt, shared by many scientists, do not constitute a "controversy," and those who feel as does the Scientific Advisory Board will not be driven into admitting it to be such.

There has been no organized effort or campaign to claim that tobacco has been proved innocent, because those who, like the Scientific Advisory Board, desire a full and complete analysis of its effects are still in search of the answers. Similarly, there has been little widely publicized presentation of negative evidence relating to tobacco use, such as there has been of reports by those who are already convinced that they have found proof of its guilt. This is not surprising, for it is satisfying to proclaim you have surrounded the enemy and that mopping up activities are all that is needed. But to state that strong enemy forces are still undetected and that a long hard campaign lies ahead is irritating to the generals who are claiming the victory.

It seems, however, to those who will have some responsibility for the continued campaign, that the public—the troops on the firing line—deserve to be told what the whole evidence is and of the likelihood that the battle is not won and then be allowed to decide for themselves what the dangers, real or imaginary, may be.

About fifteen years ago there were headlines and a propaganda flurry based on statistical evidence that direct exposure to sunlight was a causative factor in skin cancer. This point of view, which was widely accepted, received support from experiments showing skin cancer on the ears of rodents following exposure to ultraviolet light, a component of sunlight. In spite of this, no one asked for legislation to bring back the bathing regalia of the gay nineties, and no one attempted to educate children not to visit beaches or to wear sun suits, nor were farmers and sailors urged to carry umbrellas.

From the first charges that tobacco might be a causative factor in lung can-

cer and cardiovascular disease, there have been repeated efforts by some ardent laymen and some already convinced scientists to activate debate and controversy with those who desire further information before they feel ready to take the trip to Canossa.

It may be that some day—perhaps soon, perhaps years from now—we shall know what part or parts various factors play in the etiology of lung cancer in man. When we do, tobacco use may or may not prove to be one of them.

Today, while we are making real progress in lifting the cancer curtain, we should not be misled into thinking that one glimpse behind a raised corner of this curtain reveals to us all the knowledge that remains to be unearthed.

The public has been heavily propagandized along one definite theory of causation by those convinced by one level of information. Some of us demand a different order and level of knowledge before we accept causation or condone presentation of conclusions to the public. We claim merely the right to pursue knowledge through scientific research, the right to hold our point of view, and the right of the public to be aware of it.

Calm Deliberation

I have been resistant to a ready acceptance of the association between cigarette smoking and bronchogenic carcinoma. I have searched the literature for other reasonable explanations for recognizable fallacies. I have found none of importance. As of today, I must agree with many of the specialists in statistical analysis and in the epidemiology of cancer, that this associaton has been established. It was about 150 years after Percivall Pott explained the etiology of chimney-sweep's cancer and prescribed methods for its prevention before carcinogens were demonstrated in soot. . . . May we show the same practical sense as our forefathers, and not look for direct proofs which are out of reach before we transmit experience into practical measures.

Weller, C. V.: Causal Factors in Cancer of the Lung. Springfield, Ill. Charles C Thomas. 1955; p. 99.

Magnanimous Parsimony

In 1954, when interest was renewed in cigarette smoke as an etiologic factor in lung cancer, the following firms formed the Tobacco Industry Research Committee:

The American Tobacco Company, Inc.
Benson & Hedges
Bright Belt Warehouse Association
Brown & Williamson Tobacco Corporation
Burley Auction Warehouse Association
Burley Tobacco Growers Cooperative Association
Larus & Brother Company, Inc.
P. Lorillard & Co.
Maryland Tobacco Growers Association
Philip Morris & Co., Ltd., Inc.
R. J. Reynolds Tobacco Company
Stephano Brothers, Inc.
Tobacco Associates, Inc.
United States Tobacco Company

This committee appropriated funds for "research into all phases of tobacco use and health" and set up, to administer these funds, the Scientific Advisory Board with Clarence C. Little, Scientific Director of TIRC, as Chairman, Robert C. Hockett as Associate Scientific Director, and the following unsalaried members: McKeen Cattell, Julius H. Comroe, Jr., Leon O. Jacobson, Paul Kotin, Kenneth Merrill Lynch, Stanley P. Reimann, William F. Rienhoff, Jr., and Edwin B. Wilson.

In the first three years of operation TIRC has "appropriated" $2,200,000, and in the same period just 2 of the 14 member firms appropriated for advertising about $180,000,000 of their $6,000,000,000 from cigarette sales—a minuscule percentage (approximately 0.005) of sales for research—1 cent from each 1400 to 1500 packs.

Changes in the Bronchial Epithelium in Relation to Smoking and Cancer of the Lung

Oscar Auerbach, M.D., J. Brewster Gere, M.D., Jerome B. Forman, M.D., Thomas G. Petrick, M.D., Harold J. Smolin, Ph.D., Gerald E. Muehsam, M.D., Dicran Y. Kassouny, M.D., and Arthur Purdy Stout, M.D.

The high incidence of bronchogenic carcinoma in association with cigarette smoking has stimulated this study. It is based on the hypothesis that if the products of tobacco smoke are carcinogenic, their application to a tissue such as the tracheobronchial epithelium should produce a number of widespread changes such as hyperplasia, metaplasia, and neoplasia. Therefore, in a study of tracheobronchial epithelium one should expect to find these changes in the intact bronchial epithelium of persons who died of bronchogenic carcinoma and similar changes, but to a lesser degree, in the bronchial epithelium of persons who died of some other cause, but have been exposed to the same potential carcinogenic agents, in this case, tobacco smoke.

In previous reports from this institution (abstracts, *CA* 6:151, 1956; 7:182, 1957), in which histological examination of step sections of the major portion of the tracheobronchial tree was done, it was shown that three important changes occurred in the bronchial epithelium. These were basal-cell hyperplasia, stratification, and squamous metaplasia. It was found that there was a definite increase in the incidence of these changes in the bronchial epithelium of heavy smokers (including patients with bronchogenic carcinoma, all of whom were smokers) as compared to non-smokers.

The present study is a continuation of this work utilizing the tracheobronchial trees of 117 cases. As in the previous study, the tracheobronchial tree was divided into 208 serial sections all of which were examined microscopically.

Laboratory Service, Veterans Administration Hospital, East Orange, New Jersey.

The changes were classified as basal-cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ. Basal-cell hyperplasia is diagnosed when there are more than three rows of basal cells present supporting the superficial layer of tall columnar, ciliated cells. Stratification indicates an absence of the superficial layer of ciliated cells with replacement by flattened epithelial cells, but never with involvement of the deeper layers. With squamous metaplasia the flattened epithelial cells are present down to the basal layers; prickle cells are often present, and the epithelium resembles that of squamous type seen in other areas of the body. Our criteria for carcinoma in situ are the same as those described for other sites of the body such as the cervix.

In this series of 117 patients there were 34 who died of bronchogenic carcinoma of whom 19 had smoked more than one pack a day, 10 less than one pack a day,

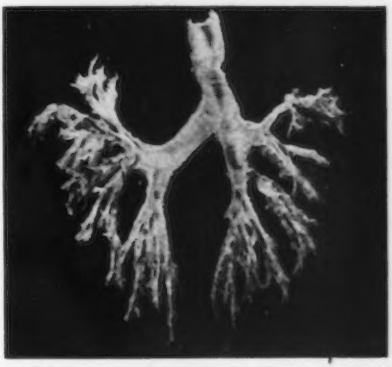

Fig. 1. Coronal section of the anterior half of the tracheobronchial tree.

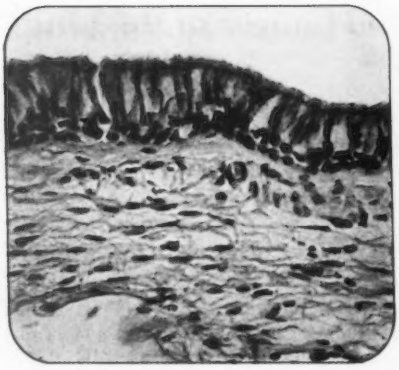

Fig. 2. Normal ciliated columnar epithelium (×200).

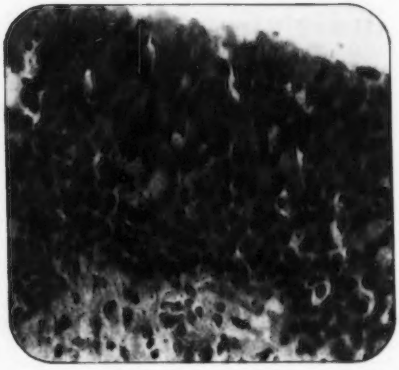

Fig. 3. Basal-cell hyperplasia (×200).

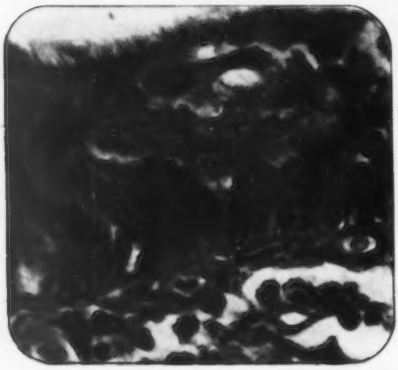

Fig. 4. Atypical basal cells (×375).

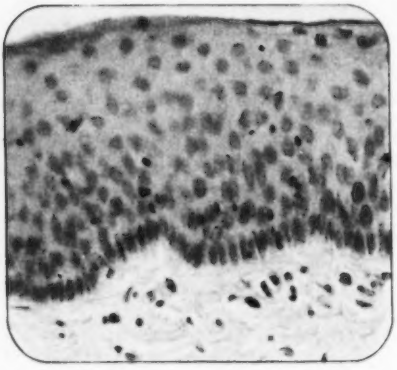

Fig. 5. Squamous metaplasia (×200).

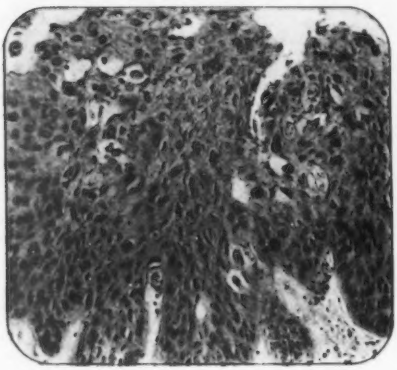

Fig. 6. Carcinoma in situ (×150).

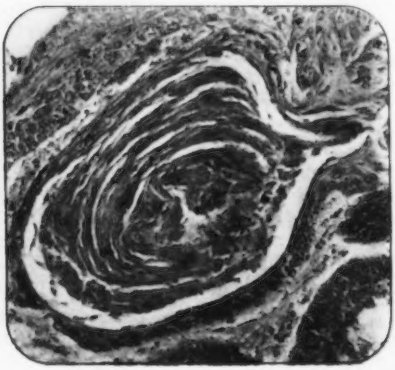

Fig. 7. Carcinoma in situ (×100).

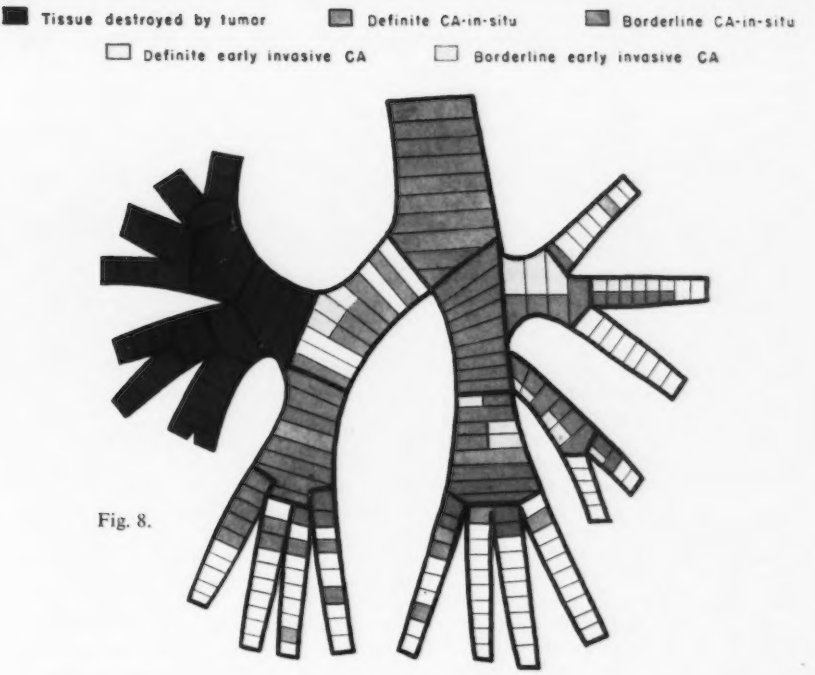

Fig. 8.

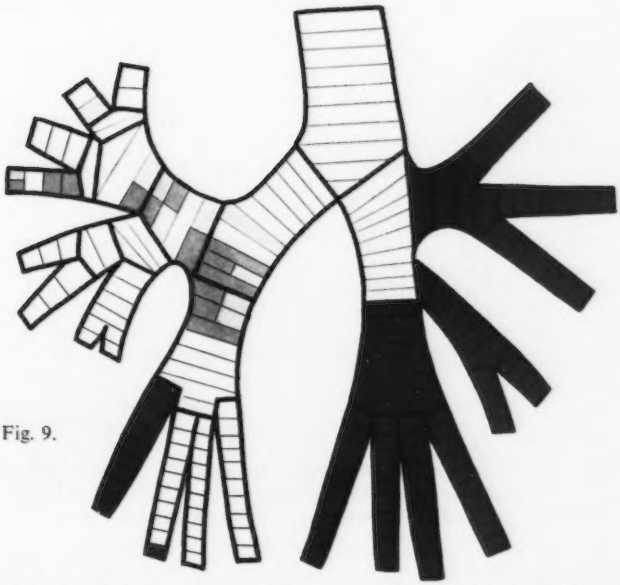

Fig. 9.

Figs. 8 and 9. Schematic drawings of two cases showing the distribution of carcinoma in situ and early invasive carcinoma in the tracheobronchial tree.

while four were ex-cigarette smokers, and one had smoked a pipe and cigars, but no cigarettes. In the nonlung cancer group there were 16 nonsmokers, 20 who smoked less than one pack a day, and 47 who had smoked more than one pack a day.

The epithelial changes were tabulated with the following results given as percentage of slides examined: basal-cell hyperplasia in the noncancer group, nonsmokers 18.6 per cent, less than one pack a day group 22 per cent, more than one pack a day 36.1 per cent, and in the lung-cancer group 43.5 per cent. Stratification in the nonlung cancer group, nonsmokers 4.2 per cent, less than one pack a day 7.1 per cent, more than one pack a day 10.4 percent, and in the lung-cancer group 13.4 per cent. Squamous metaplasia in the noncancer group, nonsmokers 1.9 percent, less than one pack 6.3 per cent, more than one pack 9.5 per cent, and in the lung-cancer group 11.7 per cent. Definite carcinoma in situ in the nonlung cancer group, nonsmokers 1.0 per cent, less than one pack a day 4.1 per cent, more than one pack a day 6.0 percent, and in the lung-cancer group 6.8 per cent.

Thus it is shown that the incidence of epithelial changes of the tracheobronchial mucosa including carcinoma in situ bears a direct relationship to the consumption of cigarettes.

As an extension of this problem it was decided to make a similar study of 54 patients dying of carcinoma of the lung to determine (1) the incidence of carcinoma in situ, (2) the distribution of carcinoma in situ in the anatomical divisions of the tracheobranchial tree, (3) whether early invasive carcinoma occurs in remaining portions of the tracheobronchial tree, and (4) the possible clinical value of these findings.

Carcinoma in situ, both definite and borderline, occurred in 17 per cent of 7993 usable slides examined in this series or in 48 of the 54 cases (89 per cent). The in situ changes were widely distributed in an irregular fashion throughout all sections of the tracheobronchial tree. There was a comparable incidence of these lesions in the lung opposite to that involved by the overt carcinoma.

Early invasive carcinoma was observed in 5 of the 54 cases. These foci were present in areas showing carcinoma in situ suggesting that carcinoma in situ is a stage prior to invasive carcinoma. The widespread distribution of all these changes point out one possible reason for the discouragingly low cure rate of carcinoma of the lung. It is felt that some cases that are clinically considered as recurrent or metastatic carcinoma of the lung may actually be foci of carcinoma in situ which have gone on to invasive carcinoma.

Other factors have been considered as possible etiologic agents for these changes, but this study has dealt only with the relationship to tobacco consumption. Our findings are considered to be fully consistent with the hypothesis that inhalation of tobacco smoke is an important factor in the causation of bronchogenic carcinoma.

There are few, if any, simple or single causes in biology; there are, instead, complex situations and environments in which the probability of certain events is increased. In most biological and sociological phenomena, the word "cause" is a semantic trap.

Shimkin, M. B.: Hormones and neoplasia. In Raven, R. W., Ed.: Cancer, *Vol. 1. London. Butterworth & Co., Ltd. 1957; p. 161.*

Report of Study Group on Smoking and Health: Section on Lung Cancer

The Study Group on Smoking and Health was organized in June 1956, at the suggestion of the American Cancer Society, The American Heart Association, The National Cancer Institute, and the National Heart Institute, to review the problem of the effects of tobacco smoking on health and to recommend further needed research to the sponsoring organizations.

The Study Group has held six 2-day conferences, has examined the pertinent literature and more recent unpublished reports, and has consulted with scientists representing specialized areas of research concerned with the subject.

The Study Group, cognizant of the implications of its conclusions and recommendations, now submits the following joint report.

LUNG CANCER [epidermoid and undifferentiated types, but not adenocarcinoma]

At least 16 independent studies carried on in five countries during the past 18 years have shown that there is a statistical association between smoking and the occurrence of lung cancer.

Fourteen [6, 13, 27, 30, 35, 37, 39, 43, 44, 45, 48, 49, 53, 54] of the retrospective studies have been reviewed by Cutler, Stocks and Campbell have studied the association between smoking and lung cancer in terms of place of residence. An additional recent retrospective study by Wynder[52] is concerned with the occurrence of lung cancer in women.

These retrospective studies have been reinforced by two investigations in which large male populations have been followed prospectively. Lung cancer occurs much more frequently (5 to 15 times) among cigarette smokers than among nonsmokers, and there is a direct relationship between the incidence of lung cancer and the amount smoked. It is estimated that on a lifetime basis, one of every ten men who smoke more than two packs a day will die of lung cancer. The comparable risk among nonsmokers is estimated at one out of 275.

Doll and Hill[14] in England and Hammond and Horn in this country reported their first results in 1954. Since then, Doll and Hill have published a follow-up report,[15] and Hammond has reported additional data.[20] Although the statistical evidence has often been quoted as indicating an association between HEAVY smoking and lung cancer, there is no evidence of a threshold level below which the risk disappears. The best available estimates for both the United States and England indicate that the lung cancer risk is statistically significant for half-pack-a-day smokers and that there is a correlation of risk with amount smoked.[15, 20, 46]

Self-selection and sampling bias have been mentioned as possible sources of error. Examination of the evidence shows that any distortion resulting from these sources does not invalidate the conclusions.

By numerical illustration, Berkson has indicated that, in epidemiologic studies similar to the one conducted by Hammond and Horn, it is possible to obtain a spurious statistical association between smoking and a disease as a result of sampling bias, even though no real association exists. It has been pointed out by Cornfield, Korteweg, Levin, and Lilienfeld that, in order for the degree of association between cigarette smoking and lung cancer observed by Hammond and Horn to be a result of sampling bias, it would be necessary to assume an unreasonably large degree of such bias. Furthermore, a study of smoking habits of a probability sample of the United States population reported by Haenszel and associates[18] indicates that the necessary degree of sampling bias was not present in the Hammond-Horn study. Berkson also indicated that the influence of sampling bias would disappear with the passage of time. Doll and Hill[15] have recently reported that, over a 4-year period of observation, the gradient of lung cancer mortality in relation to the amount smoked has remained remarkably constant during each of the four years. The issue of self-selection is raised as an argument against interpreting the statistical association of cigarette smoking and lung cancer as a causal relationship. Self-selection assumes that there is a factor that both

causes a person to smoke and causes lung cancer; thus, individuals are selected for both smoking and lung cancer by a third mutually related factor. Such a hypothesis does not appear likely. Doll and Hill[15] and Levin[31] have indicated that such a hypothesis would be inconsistent with the marked increase of lung cancer mortality in recent years. The likelihood of this hypothesis is diminished further by the biological and pathogenetic evidence discussed in this statement. However, information concerning the characteristics of smokers and nonsmokers would be valuable for further evaluation of this theoretical possibility.

Epidemiologic studies also indicate that cigarette smoking cannot account for all cases of epidermoid cancer of the lung. There are other causative environmental factors, the most important of which are probably various atmospheric pollutants. As in other diseases, various other influences, such as sex, nutrition, and heredity, may modify its occurrence.

Epidemiologic studies indicate that cigarette smoking cannot account for all cases of lung cancer; nonsmokers do develop lung cancer, and variations in frequency of lung cancer in different population groups are not completely related to variations in frequency of cigarette smoking. The most significant observation on this point is the higher death rate from lung cancer in urban, as compared with rural, areas.[17, 19] This excess urban death rate has been attributed by most investigators,[24, 26, 46] to the probable influence of air pollution. As has been indicated by Hammond[19] and by Haenszel and Shimkin,[17] part of this urban excess may be attributed to the higher proportion of cigarette smokers among urban populations, but they have also pointed out that even after adjustment has been made for differences in smoking habits, the urban rate is still higher than the rural rate. Estimates have been made of the relative contribution that cigarette smoking and the "urban factor" (probably air pollution) make to the lung cancer deaths. From studies in Liverpool, Stocks and Campbell have estimated that 50 per cent of the lung cancer deaths result from smoking and about 35 per cent from air pollution. Hammond[19] estimated that about 31 per cent of lung cancer deaths are due to air pollution. It is recognized that these estimates may not be very precise, but they do afford some idea of the relative importance of these two factors. Recently, Hueper and Kotin have defended their views that air pollution is the MAJOR ETIOLOGIC FACTOR in lung cancer and that cigarette smoking plays a minor role, if any. Cigarette smokers have higher lung cancer death rates than nonsmokers in urban areas, where presumably both of these groups have had similar exposure to general air pollution. A definite need exists for determining the chemical nature of these pollutants and estimating more precisely the role of air pollution, particularly in relation to the effect of cigarette smoking. Several studies indicate that occupational exposure to chromate ore,[2] radioactive dust, and other agents[24] increases the risk of lung cancer. However, specific occupational exposures have been demonstrated to be responsible for only a small percentage of lung cancer deaths. It is also possible that additional factors increase host susceptibility to these environmental factors. There is suggestive evidence that hormonal factors may have some influence.[32] The possible existence of endogenous factors that influence susceptibility to exogenous agents should be further investigated, since such information may have some bearing on control efforts.

The two prospective studies further suggest that cessation of smoking by chronic smokers decreases the probability that such individuals will develop lung cancer. The epidemiologic evidence is supported by laboratory studies on animals. At least five independent investigators have produced malignant neoplasms by tobacco smoke condensates. Although the active material has not been identified chemically, some progress has been made in localizing the activity in purified fractions.

In addition to the five recent demonstrations of carcinogenic activity in tobacco smoke,[23, 38, 40, 47, 55] Roffo and Woglom had previously reported the production of cancers from tobacco tar. Evidence for a cocarcinogenic effect of tobacco smoke condensate has been obtained by Gellhorn. Several workers have now reported the presence of 3,4-benzopyrene in tobacco smoke.[5, 7, 10, 29, 56] This has been demonstrated to be present in the neutral fraction of tobacco smoke condensate at concentrations of about two micrograms per 100 cigarettes. According to Wynder, the concentration is so low that the biological activity observed in his most purified fractions cannot be the result solely of 3,4-benzopyrene. Other carcinogenic polycyclic hydrocarbons are being sought. In addition to 3,4-benzopyrene, Bonnet and Neukomm found other polycyclic hydrocarbons, including 3,4,9,10-dibenzopyrene at an estimated

concentration of one microgram per 100 cigarettes. Recently Lacassagne and others produced sarcomas in mice by three subcutaneous injections totaling 1.8 milligrams of this compound per animal. The quantitative aspects of this problem obviously should be investigated.

Although the demonstration of carcinogenic activity in animals does not constitute proof of carcinogenicity in the lungs of human beings, this is important contributory evidence that strengthens the concept of causal relationship.

Studies on pathogenesis of human lung cancer are also compatible with the causal relationship. Physiologic observations indicate that foreign material is trapped in the tracheobronchial tree, particularly where ciliary action is inhibited or the ciliated epithelium is destroyed.

In the normal human lung, particulate matter, upon inhalation, may penetrate diffusely throughout and into the alveoli. This is evident from many observations, both clinical and experimental. Robertson, in an exhaustive investigation and review of this subject, presents evidence to indicate that such factors as particle size and concentration and the depth of ventilation, as well as time of exposure, are important determinants of the amount of particulate matter that will enter the lung. It is estimated that the range of particulate size in cigarette tobacco smoke is between 0.3 and 1.0 micron. Particles of this size, upon inhalation, may readily be distributed diffusely throughout the lung. Increased depth of ventilation, such as is seen in inhalation during smoking, favors the entrance of greater amounts of particulate matter into the lungs. Particles that penetrate the upper air passages come in contact with the mucus-covered surface of the bronchi, where they tend to adhere and to remain in contact with bronchial mucosa for varying periods of time, depending on the size and nature of the particles. An irritant such as smoke may bring about alterations in the ciliary activity of the bronchial mucosa. It is this ciliary activity that is the main mechanism available for the removal of particulate matter from the lung.[34] Slight temporary alteration in this ciliary activity will allow for the retention of particulate matter. Furthermore, any alteration in the quantity or quality of mucus in the tracheobronchial tree will also interfere with the removal of particulate matter. Particles may become concentrated in outdrifting mucus and remain in contact with bronchial mucosa for significant periods of time. Hilding demonstrated the possible role of paralyzed cilia or deciliated areas in the accumulation of cigarette tar by exposing recently removed calf lungs to cigarette smoke.

Fluorescent substances present in cigarette smoke have been shown to enter the cells of the buccal mucosa.

After smoking, according to the degree of keratinization, some chronic cigarette smokers who were tested were found by Mellors and others to have fat-soluble fluorescent substances in scrapings of the buccal mucosa. Such substances are not observed, to any appreciable degree, 12 hours after smoking.

Detailed histologic studies of the tracheobronchial tree indicate that basal cell hyperplasia, atypical hyperplasia, squamous metaplasia, and areas of morphologic alteration with all characteristics of carcinoma in situ are encountered more frequently among cigarette smokers than among nonsmokers.

It is well established that changes may be observed in epithelial surfaces that precede established forms of invasive carcinoma. These alterations consist of atypical hyperplasia, metaplasia, and carcinoma in situ. Although there may be disagreement in the terminology in these early morphologic changes, their presence and significance are generally accepted. It has been demonstrated by Black and Ackerman that epidermoid carcinoma in situ is an important stage in the histogenesis of lung cancer. If smoking is related causally to the development of epidermoid carcinoma of the lung, then one would expect to find a greater incidence of these early morphologic changes in the bronchial tree in smokers than in nonsmokers. A study investigating this hypothesis was carried out by Auerbach and associates. A total of 28,638 slides were made from the tracheobronchial tree of 150 autopsied individuals in whom a cigarette-smoking history had been obtained. Such changes as basal cell hyperplasia, stratification, squamous metaplasia, and carcinoma in situ were found, both quantitatively and qualitatively, to a significantly greater degree in smokers than in nonsmokers. The findings were accentuated in autopsied cases of bronchogenic carcinoma; all such patients had been smokers. Carcinoma in situ was found in one per cent of the slides of those who did not smoke regularly whereas it was found in 6 per cent of the slides in those individuals who smoked more than one pack of cigarettes a day. Determination of the

incidence of the various stages of these lesions, as related to sex, age, and exact anatomic distribution, awaits the investigation of larger numbers of cases. The alterations recorded by Auerbach were similar in almost all details to those that are found to precede and develop into epidermoid carcinoma of the uterine cervix. Chang and Chang and Cowdry studied whole mounts of bronchial epithelium obtained at autopsy from smokers and nonsmokers. They found metaplasia and thickening of the epithelium more common among the smokers than among the nonsmokers. These results are in good agreement with those of Auerbach. In addition, they observed that the cilia were shorter and that goblet cells were more numerous in the lungs of smokers than in those of nonsmokers.

Thus, every morphologic stage of carcinogenesis, as it is understood at present, was observed and related to the smoking habit.

The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung.

The evidence of a cause-effect relationship is adequate for considering the initiation of public health measures. Nevertheless, additional research is needed to clarify many details and to aid in the most effective development of a program of lung cancer control. The need for information in the following areas appears to be very important: (1) The isolation, identification, and possible elimination from tobacco smoke of chemicals that produce cancer in animals.

> It is possible that an innocuous cigarette could be developed without prior identification of the active agents, and efforts along this line should parallel the work on characterization of the active materials. However, if empiric reduction is achieved, it would still be urgent to define the chemical nature of the agents and their mode of action. Reduction in tumor activity might be sought by the removal or inactivation of carcinogenic, cocarcinogenic (promoting) factors or the precursors of either. Possibilities that suggest themselves include selection of tobacco strain, extraction of tobacco leaves, alteration of the burning temperature of the cigarette, and, possibly, selective removal of the active material from tobacco smoke. In this connection, it should be noted that the filters that are presently in use do not appear to be selective in their action; rather, they reduce tumor activity only to the extent that they remove whole smoke.[51] In the case of most commercial cigarette filters, efficiency is not high, and accordingly the amount of smoke that reaches the lungs is not reduced to any major degree. An incidental but urgent requirement for the identification studies is improved assay procedures, since the work is at present hampered by the necessity for relying on slow and relatively insensitive methods.

(2) The role of atmospheric pollutants and additional environmental factors other than cigarette smoking in the causation of lung cancer in man. (3) The effect of cessation of smoking on the occurrence of lung cancer in man.

> The most desirable method of obtaining information concerning the effect of cessation of smoking would be by an experiment with human beings. A description of one of several designs follows. A group of smokers, who would volunteer to be included in the study, would be randomly allocated to an experimental and a control group. The control group would continue to smoke, whereas the experimental group would be asked to give up smoking. These groups would be followed for a number of years to determine the risk of dying, in general, and the risk for specific causes of death. Even though all individuals in the experimental group had not ceased smoking, comparisons of mortality rates in the two groups would be made. Obviously, success of the experiment would depend on the proportion of the experimental group who had stopped smoking; if it is 50 per cent or more, meaningful results could be expected. Consideration of sample sizes required for this experiment indicated that very large samples would be necessary to obtain results with respect to lung cancer because of the relatively low death rate from this cause. However, the estimated sample sizes for studying the effect of cessation of smoking on total mortality . . . appeared to be within practical limits; at least, they were such that further exploration of the feasibility of such an experiment appears warranted. Prior to conducting a full-scale experiment, a pilot study should be undertaken. Such a study is important, not only from a biological viewpoint but also from a public health administrative viewpoint, in that it would be a means of evaluating the feasibility of certain control efforts. It should be recognized, of course, that such an experiment would fail to show a difference between

experimental and control groups if the damage to the organ system had been irreversibly established at the time smoking was stopped. Further information on the effect of cessation can be obtained from the prospective studies of Hammond, Doll and Hill, and from the Veterans' Study that is now being conducted by the National Institutes of Health. It is recommended that collection of the necessary data continue to be made with respect to this aspect of these studies.

(4) Measurement of possible physiologic, sociologic, and psychologic differences between smokers and nonsmokers and the relation of host differences to the occurrence of lung cancer.

A large prospective study of the effect of smoking on lung cancer and other causes of death among approximately 220,000 veterans of World War I is now in progress, at the National Institutes of Health, under the direction of Harold F. Dorn. This study offers an excellent opportunity to explore, by additional questionnaires and interviews, some of the possible differences that may exist between smokers and nonsmokers. In addition, this study could also be expanded to include cardiovascular evaluation, perhaps even to the extent of including physical examinations and laboratory determinations on subsamples of the smoker and nonsmoker groups. The study group has been in contact with Dorn and has suggested that additional questionnaires and clinical and laboratory determinations might be valuable. It is hoped that these suggestions will be developed into research actions with the help of the National Heart Institute and the U. S. Veterans Administration. There is no evidence at present to indicate that the occurrence of cancer of the lung among cigarette smokers is limited to an undefined subgroup of susceptible individuals. Nevertheless, certain characteristics may well be correlated with greater or less susceptibility to lung cancer or heart disease. Research on host factors that may be associated with, or modify, certain disease states is of great importance. This is particularly true of chronic diseases in which the etiologic situations are often multiple and in which the host response may play a paramount role.

Conclusions

The study group concludes that the smoking of tobacco, particularly in the form of cigarettes, is an important health hazard. The implications of this statement are clear in terms of the need for thorough consideration of appropriate control measures on the part of the official and voluntary agencies that are concerned with the health of the people. The lack of specific recommendations in this regard reflects no lack of interest. Rather, it reflects the desire of the study group to limit its recommendations to the area of research needs in accordance with the instructions it received. The study group recommends that further research on smoking and health be vigorously pursued. The recommendations made in the section on "Lung Cancer" are for research into means of coping with lung cancer hazard, which has been established for cigarette smoking. The Study Group on Smoking and Health approves dissemination of this report as desired by the sponsoring agencies and hereby terminates its activities.

[References available on request.]

"Might of Right"

When the case is proved, and the hour is come, justice delayed is justice denied.
—William Ewart Gladstone.

The evidence that led to the passing of legislation concerning benzol, aniline and a host of other dangerous industrial solvents is of exactly the same type as that which incriminates cigarette smoking as a factor in the genesis of carcinoma of the bronchus.

Anon.: Lung cancer. [Commentary.] Brit. J. Clin. Pract. 11:80, Jan., 1957.

CANCER CLINIC

Pulmonary Cancer With Special Reference to Air Pollution and Pathogenesis*

Dr. Kotin: A discussion of environmental agents associated with the initiation of lung cancer should be centered around an appraisal of the mechanisms whereby these factors can play a role in cancer induction. The mere demonstration of a hazardous agent in the environment does not inevitably imply a biological threat. As there is nothing known at present to indicate an unusual natural history for lung cancer when compared with other visceral cancers, a preliminary general discussion of carcinogenesis seems advisable. The interval required for neoplasms to develop clinically is so great and our knowledge of critical carcinogenic doses is so small that we must err on the side of conservatism and assume that the environmental presence of any carcinogen is at least theoretically synonymous with an adverse effect. While at present we know of no tolerable doses of a carcinogen, certain modifying factors tend to incriminate some environmental sources more than others. These factors include the quantity of carcinogen present, the chemical nature of the carcinogen, the physical state in which it exists, the frequency and intensity of host exposure, and the ability of the host to marshal defensive or neutralizing powers.

The industrialization and urbanization of society have resulted in an ever-increasing pollution of the atmosphere with car-

*Paul Kotin, M.D., Hans L. Falk, Ph.D., and Charles J. McCammon, M.D. From a staff and teaching conference of the Department of Pathology, University of Southern California School of Medicine, Los Angeles, Calif.

cinogenic agents. Exhaust products of gasoline and diesel engines, certain industrial effluents, the incomplete combustion products of petroleum and coal and many of their by-products used in construction and road paving are some of the major sources of these pollutants. Dr. Falk will discuss some of the chemical and physical properties that have been identified in the atmosphere.

Dr. Falk: Carcinogenic agents belonging to the group of polycyclic aromatic hydrocarbons, to the aliphatic epoxides, and to inorganic compounds containing chromium and nickel have been identified in the atmosphere. One of the most ubiquitous of the carcinogenic agents belonging to the polycyclic aromatic hydrocarbon group of chemicals is 3,4-benzpyrene. It is derived as an atmospheric pollutant from many sources including gasoline and diesel engine exhausts, soot secondary to the incomplete combustion of organic matter, soot incidental to rubber-tire wear and tear and degradation, and in isolated areas as specific industrial effluents in the manufacture of coal tar and its derivatives. The aliphatic materials are primarily introduced into the atmosphere as a result of pollution by raw gasoline vapors. These vapors, under certain meteorologic conditions, react in the presence of sunlight and oxides of nitrogen to form a broad spectrum of hydrocarbon oxidation products. Chromium and nickel though present in infinitesimal amounts nevertheless must be considered by virtue of occupational and experimental data incriminating them as carcinogenic agents. It must be remembered that one of the critical factors in eliciting the carcinogenic responses is the concentration at which these agents are present.

3,4-Benzpyrene usually exists in the atmosphere adsorbed on soot. It has been shown that prior to producing a carcinogenic response this soot must release this carcinogen. A significant factor controlling the ability of the soot to give up its benzypyrene is its particle size. Soots in the size range compatible with this property have been recovered from the air. Following inhalation, a period of contact with the respiratory-tract epithelium is necessary for the carcinogen to be liberated and enter the cell, thereby providing a carcinogenic stimulus. Ordinarily this prolonged interval of contact with the respiratory epithelium is precluded by the physiologic defenses existing in the tracheobronchial tree. Under certain conditions, however, the host defenses can be interfered with and abnormally long residence of particles ensues.

Dr. Kotin: As Dr. Falk has mentioned, a sequence of atmospheric presence of the carcinogenic agents, their respiration, and the interference with normal host resistance factors represents the constellation necessary for initiating the carcinogenic processes. Now what are these defense mechanisms?

Dr. McCammon: The principal and most potent factors responsible for the prevention of prolonged residence of particles on the lining cells of the tracheobronchial tree are the stream of mucus covering the epithelial cells and the activity of ciliated cells, which by their action constantly move the mucus cephalad. Particles settling out on this stream are as a result immediately set in motion. The normal rate of movement of these settled particles is sufficiently rapid so that carcinogenic action in the tracheobronchial tree is unlikely to occur under physiologic conditions. The initial period required for elution or removal of the carcinogen from the soot and the added time required for entry into the cell can obtain only when the ciliary-mucus defense barrier is weakened or lost. Carcinogenic particles penetrating more deeply into the pulmonary parenchyma to the level of the alveoli are subject to ingestion by the macrophage in the lungs. Phagocytosis is effective in removing these particles which are then ultimately disposed of by entry into the systemic lymphatics or by being advanced to the level of the stream of mucus.

Dr. Falk: Of significance is the fact that the soot particle with its adsorbed 3,4-benzpyrene undergoes change within the cytoplasm of the macrophage. Actually, the adsorbed 3,4-benzpyrene is eluted or washed off the soot particle and made

available for protein binding and a presumed biological action.

Dr. Kotin: Dr. Falk, would you continue by discussing the substances capable of interfering with normal secretion of mucus and ciliary activity?

Dr. Falk: Numerous irritants of a nonspecific type are present in polluted atmosphere, which when breathed in sufficient concentration, are capable of first slowing the flow of mucus and ultimately stopping ciliary activity. These compounds include both organic and inorganic acids, the oxidation products of hydrocarbons, aldehydes, the oxides of nitrogen, and the oxides of sulfur. These may be present in the air as gases and aerosols. As a rule, the effect of these compounds is transient and when their concentration drops, normal activity returns. Under some circumstances these irritants may produce an initial short period of increased flow of mucus which is then followed by a decrease and, perhaps, ultimate cessation. In so far as secretion of mucus is concerned, the mucus-secreting cells first react to the irritants by hypersecretion, after which a form of exhaustion apparently occurs, and both the mucous cells and the adjacent ciliated cells may desquamate down to the level of, but not including, the basal cells. The exposure of the basal-cell layer creates an additional hazard in that carcinogenic material is then in direct apposition to the cell layer which presumably gives rise to hyperplastic, metaplastic, and ultimately neoplastic change.

This phenomenon is of considerable interest in that we have a link in the pathogenetic sequence in which compounds which are in themselves noncarcinogenic theoretically make possible, in the respiratory tract, the biological activity of chemical compounds endowed with the property of inducing cancer.

Dr. Kotin: It appears now that the pollution of the air by carcinogenic hydrocarbons and defense-neutralizing irritants provides the physical, chemical, and biological milieu necessary for cancer induction. The next problem is that related to the level of exposure of the general population. We are unanimous in our belief that as of the moment we must assume that any exposure is hazardous. As the carcinogenic dose is the product of the concentration of the environmental carcinogenic agent and the exposure time, current data strongly suggest that in general we are being subjected to low dosages of carcinogens. While little is really known concerning carcinogenic dosages in man, the exposure to a "low dose" over a long period of time is compatible with the induction of the neoplastic state. Abundant experimental evidence exists to indicate that this is so.

Dr. Falk: Both epidemiologic and experimental data indicate that the development of cancer usually requires a prolonged interval. In the instance of human lung cancer, a period of from ten to twenty years is postulated. This seems entirely reasonable when one considers that, experimentally, approximately twenty-five to fifty per cent of the life span of an animal is usually required for the induction of cancer. Spontaneous tumors in experimental animals usually occur in the second half of the life span. This is similar to the experience in man.

Dr. Kotin: The orientation of this discussion in the direction of assessing the role of air pollution in the pathogenesis of lung cancer should by no means be interpreted as indicating that this is the only factor of significance. On the basis of our discussions thus far, the problem of lung cancer reduces itself not only to the identification of etiologic factors or agents but rather it resolves itself into properly evaluating the significance of various factors which are seemingly associated with the onset of lung cancer. These certainly vary from case to case. In addition to air pollution, cigarette smoking has been the subject of considerable investigation. Epidemiologically, an increased liability to the development of lung cancer has been shown to exist in the instance of heavy cigarette smokers. The very existence of lung cancer in nonsmokers indicates that in any given case the stimulus that smoking represents is a deletable or nonessential one. Further, the nondevelopment of lung cancer in approximately ninety per

cent of very heavy smokers strongly indicates that whatever role cigarette smoking may play it is likely one that occurs subsequent to or in association with other carcinogenic stimuli. Conversely, the development of lung cancer in rural residents and in residents of countries that are essentially agricultural in nature indelibly suggests that air pollution alone cannot explain all lung cancer. With these facts in mind we inevitably reach an almost universal concept in medicine which recognizes that any given biological phenomenon rarely occurs in response to one and only one stimulus.

It would be well before concluding this clinic to review the presence of carcinogenic agents in some of our more universal sources. Dr. Falk, you mentioned that 3,4-benzpyrene is certainly the most ubiquitous of our known carcinogenic hydrocarbons. Despite our limited knowledge, do you feel that its presence in our environment is in sufficient quantity to be of significance in the increasing incidence of lung cancer?

Dr. Falk: Yes. Although it is not the only carcinogenic polycyclic hydrocarbon in our atmosphere, it is the one that is both most potent and most readily available to the host. Even after correcting in a loose way for all the variables, the presence of 3,4-benzpyrene in soot in our atmosphere probably represents the largest single and most universally available source of this potent agent. Other environmental sources of 3,4-benzpyrene include occupational exposure in workers in gas retort operations, gas coking plants, oil shale processing, and asphalt and tar manufacture. On a more general level, exposure also occurs in cigarette smokers.

Dr. Kotin: Lung cancer represents one of the critical problems in the field of pulmonary disease. Laboratory investigation can contribute much information to the ultimate solution of this problem despite the fact that experimental investigations are necessarily limited to animal species. It is necessary to remember certain deficiencies inherent in this discipline. Choice of species, selection of appropriate animal strain, duration of exposure, concentration of the test material, and routes of administration are all variables which modify the extrapolation of experimental data to man. Despite these shortcomings, past experience has shown a high index of significance of animal experiments for the human species. The broad spectrum of agents carcinogenic for visceral organs in experimental animals and apparently in man should make one proceed with caution in attributing the absolute dominance of any one over another. It is perhaps safest to regard the development of lung cancer as the end state of a series of sequential changes requiring the presence of a carcinogenic agent, environmental, host-modifying factors, and the innate susceptibility of the host. The links in the chain are not all of equal magnitude. Animal experimentation provides us with a tool operating to make clear the mechanisms concerned with the initiation and ultimate clinical manifestation of lung cancer. Instead of searching exclusively for a "cause" of lung cancer, it might be more rewarding to investigate the series of changes which constitute its pathogenesis.

Congressional Committee on Cigarette Industry

The report of the Subcommittee of the House Government Operations Committee, headed by Representative Blatnik (D., Minn.), blasts the Federal Trade Commission for "weak and tardy action" against the tobacco industry for having "deceived the American public through their advertising of filter-tip cigarettes." The report also criticises the industry for ignoring "repeated invitations to appear" before the committee. "It is indeed most reprehensible that the tobacco industry should so shirk its vast responsibilities to the consumer and apparently conspire to boycott the hearings of a congressional committee."

Tobacco Smoking and Cancer of the Lung

Statement of the [British] Medical Research Council

The Increase in Lung Cancer

In their annual report for 1948-50 the Council drew attention to the very great increase that had taken place in the death-rate from lung cancer over the previous twenty-five years. Since that time the death-rate has continued to rise, and, in 1955 it reached a level more than double that recorded only ten years earlier (388 deaths per million of the population in 1955 compared with 188 in 1945). Among males the disease is now responsible for approximately 1 in 18 of all deaths. Although the death-rate for females is still comparatively low, it also has shown a considerable increase in recent years and the disease is now responsible for 1 in 103 of all female deaths.

Three comments may be made on these figures. In the first place, the trend over the last few years indicates that the incidence has not yet reached its peak. Secondly, the figures are not to be explained as a mere reflection of the introduction and increasing use of improved methods of diagnosis but must be accepted as representing, in the main, a real rise in the incidence of the disease, to an extent which has occurred with no other form of cancer. Thirdly, only a small part of the rise can be attributed to the larger numbers of older persons now living in the population; in the last ten years the lung-cancer death-rates among both men and women have risen at all ages from early middle-life onwards.

Possible Causes of the Increase

The extent and rapidity of the increase in lung cancer point clearly to some potent environmental influence which has become prevalent in the past half-century and to which different countries, and presumably also men as compared with women, have been unequally exposed. The pattern of incidence of the disease rules out any possibility that the increase can be due, in a substantial degree, to special conditions, such as occupational hazards, affecting only limited groups. It is necessary to seek some factor or factors distributed generally throughout the population, and in considering the possibilities it must be borne in mind that a very long period, 20 years or more, may elapse between exposure to a carcinogenic agent and the production of a tumour. From the nature of the disease attention has focused on two main environmental factors: (1) the smoking of tobacco, and (2) atmospheric pollution—whether from homes, factories, or the internal combustion engine.

Smoking as a Cause of Lung Cancer

Epidemiological Surveys—The evidence that heavy and prolonged smoking of tobacco, particularly in the form of cigarettes, is associated with an increased risk of lung cancer is not based on the observation that the substantial increase in the national mortality followed an increase in the national consumption of cigarettes. It is derived from two types of special inquiry. In the first, the patients with lung cancer have been interviewed and their *previous* histories in relation to smoking and other factors that might be relevant have been compared with those similarly obtained from patients without lung cancer. The results of 19 such inquiries (in this country, the U. S. A., Finland, Germany, Holland, Norway, and Switzerland) have been published. They agree in showing more smokers and fewer non-smokers among the patients with lung cancer, and a steadily rising mortality as the amount of smoking increases. In the second type of inquiry, information has been obtained about the smoking habits

of each member of a defined group in the population and the causes of the deaths occurring *subsequently* in the group have been ascertained. There have been two such investigations, one in the U. S. A. covering 190,000 men aged 50-69, and the other in this country covering over 40,000 men and women whose names appeared on the Medical Register of 1951. In both, the results have been essentially the same. The investigation in this country, which has now been in progress for more than five years, has shown with regard to lung cancer in men:

(1) A higher mortality in smokers than in non-smokers.
(2) A higher mortality in heavy smokers than in light smokers.
(3) A higher mortality in cigarette smokers than in pipe smokers.
(4) A higher mortality in those who continued to smoke than in those who gave it up.

It follows that the highest mortalities were found among men who were continuing to smoke cigarettes, heavy smokers in this group having a death-rate nearly 40 times the rate among nonsmokers. Although no precise calculation can be made of the proportion of life-long heavy cigarette smokers who will die of lung cancer, the evidence suggests that, at current death-rates, it is likely to be of the order of 1 in 8, whereas the corresponding figure for non-smokers would be of the order of 1 in 300. The observation on the effect of giving up smoking is particularly important, since it indicates that men who cease to smoke, even in their early forties, may reduce their likelihood of developing the disease by at least one half.

It should be noted that the excess of deaths from lung cancer among smokers was not compensated for by any corresponding reduction in the number of deaths from cancer of other sites in the body; in other words, there was a total incidence of cancer in the smoking groups in excess of the incidence that would have prevailed in the absence of smoking.

It will be apparent from what has been said that the evidence from the many inquiries in the past eight years, both in this country and abroad, has been uniformly in one direction and is now very considerable. It has been further strengthened recently by the observation from several sources that the extent of the relationship with smoking differs for different types of lung tumour which can be distinguished only by microscopic examination.

Laboratory Evidence—From the physical and chemical point of view there is nothing inherently improbable in a connection between smoking and lung cancer. Tobacco smoke consists largely of microscopic oily droplets held in suspension in air, and these droplets are of a suitable size to be taken into the lungs and retained there. Over a hundred constituents have so far been identified and, among these, five substances have already been found which are known to be capable, in certain circumstances, of causing cancer in animals. Some workers have succeeded in producing tumours in animals by painting concentrated extracts of tobacco tar on the skin. Known carcinogens are present in tobacco smoke in very small amounts however, and there is no certainty that such low concentrations could be harmful to human beings. Nevertheless, the finding of carcinogenic agents in tobacco smoke is an important step forward, in that it provides a rational basis for the hypothesis of causation.

Atmospheric Pollution as a Cause of Lung Cancer

It has been known for some years that mortality from lung cancer is greater in urban areas than in the countryside. This fact, together with the identification of carcinogenic substances in coal smoke and in motor-vehicle exhausts, has led to the supposition that exposure to atmospheric pollution may be concerned with the increase in lung cancer. The rôle of atmospheric pollution is particularly difficult to investigate however, and the evidence is neither so consistent nor so extensive as that relating to tobacco smoking. On the one hand, no excess mortality from lung cancer has been observed in persons who would be especially exposed by the nature

of their work to atmospheric pollution—for example, transport workers, garage hands, and policemen. On the other hand, the results of a number of investigations have suggested that a relationship does exist between atmospheric pollution and lung cancer. Perhaps the best evidence for this relationship comes from studies of the small number of deaths from the disease among *non-smokers* in different types of residential district; in these studies higher death-rates have been observed among non-smokers in large towns than among those in rural areas. On balance it seems likely that atmospheric pollution plays some part in causing the disease, but a relatively minor one in comparison with cigarette smoking.

Assessment of the Evidence Relating to Smoking and Lung Cancer

Knowledge of the causation of lung cancer is still incomplete. Many factors other than tobacco smoking are undoubtedly capable of producing the disease; for example, at least five industrial causes have been recognized. Nevertheless, the evidence for an association between lung cancer and tobacco smoking has been steadily mounting throughout the past eight years and it is significant that, during the whole of this period, the most critical examination has failed to invalidate the main conclusions drawn from it. It has indeed been suggested that the fundamental cause may be some common factor underlying both the tendency to tobacco smoking and to the development of lung cancer some twenty-five to fifty years later, but no evidence has been produced in support of this hypothesis.

In scientific work, as in the practical affairs of everyday life, conclusions have often to be founded on the most reasonable and probable explanation of the observed facts and, so far, no adequate explanation for the large increase in the incidence of lung cancer has been advanced save that cigarette smoking is indeed the principal factor in the causation of the disease. The epidemiological evidence is now extensive and very detailed, and it follows a classical pattern upon which many advances in preventive medicine have been made in the past. It is clearly impossible to add to the evidence by means of an experiment in man. The Council are, however, supporting a substantial amount of laboratory research which may throw more light on the mechanism by which tobacco smoke and other suspected causative factors exert their effect, and which may thus eventually add to the degree of proof already attained as a result of studies of human populations. It must be emphasized, however, that negative results from work with animals cannot invalidate conclusions drawn from observations on man.

Conclusions

1. A very great increase has occurred during the past twenty-five years in the death-rate from lung cancer in Great Britain and other countries.

2. A relatively small number of the total cases can be attributed to specific industrial hazards.

3. A proportion of cases, the exact extent of which cannot yet be defined, may be due to atmospheric pollution.

4. Evidence from many investigations in different countries indicates that a major part of the increase is associated with tobacco smoking, particularly in the form of cigarettes. In the opinion of the Council, the most reasonable interpretation of this evidence is that the relationship is one of direct cause and effect.

5. The identification of several carcinogenic substances in tobacco smoke provides a rational basis for such a causal relationship.

That mortality from lung cancer in "heavy" smokers has been some 20 times the rate in non-smokers understates the facts of life. A pity but there it is.

Hill, A. B.: Smoking and cancer of the lung. [Letters to the Editor.] Lancet 2:1289, Dec. 21, 1957.

new developments in cancer

Air Pollution Research . . .

The second annual research planning seminar of the Air Pollution Medical Program was held at the Robert A. Taft Sanitary Engineering Center, Cincinnati, Ohio on February 3, 4 and 5, 1958. One of seven panels in the seminar was devoted to air pollution and cancer and was chaired by Dr. J. R. Goldsmith, Head of Studies on Health Effects of Air Pollution of the State of California, Department of Public Health. Dr. Norton Nelson presented the only formal paper in which he summarized some of the work which is being carried out under his supervision by Dr. M. Kuschner and others on the production of experimental bronchogenic carcinoma in mice and rats. He first pointed out the need for such studies since the chief methods currently available for testing carcinogenic activity of environmental agents involve skin painting and the production of sarcomas or of benign pulmonary adenomas in susceptible strains of mice. After numerous attempts it was found that the method described by Andervont of impregnating threads with polynuclear hydrocarbons was successful. A method using pellets made up of known carcinogens such as methycholanthrene and dibenzanthracene also produced epidermoid lung cancers. Many attempts to produce lung cancer with known carcinogens by intratracheal injections or inhalation had been unsuccessful. A tentative conclusion has been that damage to the bronchial epithelium and persistence of the carcinogen at the site of damage were both necessary for cancer production.

Dr. Dean F. Davies, discussing Dr. Nelson's paper, said that the evidence indicates that the tracheobronchial tree under ordinary circumstances is extremely efficient in removing foreign material and that Dr. Nelson had found ways of overcoming this obstacle to the production of experimental lung cancer.

In the absence of Dr. W. C. Hueper, who was to discuss carcinogenic potential of community particulate air pollutions, Dr. A. G. Gilliam pointed out a number of pitfalls which are frequently encountered in epidemiologic studies, such as those concerned with the relationship between air pollution and lung cancer. He made the clear distinction between statistical association or correlation and a causal relationship and brought out that there had been urban-rural differences presumably owing to differences in air pollution. The role of air pollution, however, cannot be studied satisfactorily without due consideration of occupational hazards and smoking habits in addition to age and sex. In discussion, Dr. Davies stated that the kind of study which seems to be indicated will encompass cooperation of a number of interested agencies, no one of which adequately covers the several facets of the problem.

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Contributed Comments*

I. Chinks in the Statistical Armor

The advocacy of a causal relationship between the smoking of tobacco and pulmonary cancer has developed some of the prodromata of an apostolic crusade, though virtually the entire basis for this belief is a statistical association. In a published review (1955) of the Hammond-Horn report (1954) Berkson, the distinguished biometrician at the Mayo Clinic, remarked that he is not affected by "the considerable number of statistical studies that have been published . . . showing an association between smoking and cancer of the lungs. On the contrary, undeviating consistency of statistical results all in support of the same conclusion is in some circumstances the hallmark of spurious statistical correlation." In 1957 Dr. Berkson, in a communication to a Congressional subcommittee, reiterated his earlier statement: "Since (1955) more data have appeared, which I have studied carefully. I find no reason to modify my previous opinion that the evidence, taken as a whole, does not establish, on any reasonable scientific basis, that cigarette smoking causes lung cancer. On the contrary, I have found more and stronger reasons to doubt this conclusion." Some of the more notable discrepancies can be listed with necessary brevity:

1. The "epidemic" increase in lung cancer may be more apparent than real, and due in great part to a wider availability of improved diagnostic skills.

2. While the proportion of women smoking has increased from less than 5 per cent to 40 per cent, lung cancer has emerged as a disease of males from an earlier ratio of 2:1 to about 6:1.

3. The median age at diagnosis has not changed.

4. Based on mass samples, correlation is lacking.

	Relative Cigarette Consumption	Relative Lung Cancer Mortality
U.S.: England	2:1	1:2
New York: Idaho	1:1	4:1
Charlotte (N. C.): Manhattan	1:1	1:4

5. The urban:rural ratio of lung cancer for *nonsmokers*, by the British Empire Cancer Campaign Report for 1956, was 9:1, or roughly the observed difference in atmospheric pollutants.

6. There is a distinct relationship between socio-economic status and pulmonary cancer, with no comparable disparity in smoking habits.

7. Experimental pulmonary carcinoma is readily evoked by an environment of artificial "smog" (Kotin and associates), while similar exposure of laboratory animals to cigarette smoke has yet to produce any significant neoplasia of the respiratory tract.

The most disturbing feature of prematurely designating tobacco as an established causative agent is an inevitable obscuration of the problems inherent in the "atmospheric sewers" of our urban areas, with a predicted increase of 30-fold in synthetic chemical manufacture alone in the next 20 years. The average urbanite inhales some 8,000 quarts of his sullied atmosphere each 24 hours. Some dilution of this noxious ambient by the ambrosial products of the solacing weed must remain as an inalienable, individual privilege. The etiologic possibilities of genetic, hormonal, and environmental factors in lung cancer are so complex that the proposal for anti-tobacco propaganda on such a basis amounts to intellectual excess.

Ian Macdonald, M.D.

Assoc. Clin. Professor of Surgery, Univ. of Southern California School of Medicine, Los Angeles.

*Opinions expressed are not necessarily those of the American Cancer Society.

II. What Can One Think?

As part of its role in the control of lung cancer the American Cancer Society disseminates the known facts derived from research concerning the causes of this disease. When the spotlight has been focused on tobacco in response to such research findings, Dr. Little has deflected the light to "many, many substances that we all use or are exposed to from day to day," and to "many variables in human habits, environments, and constitution—hormonal influences and many other factors." This leads naturally to the suggestion that the tobacco industry should support research on air pollution and that the automotive industry direct its attention to cigarette smoke. Neither wants to incriminate its own product; products of both have already been seriously incriminated.

The medical profession and the public must decide whether the partially allocated research appropriation of $2.2 million, of which so much has been made, has been more valuable as a fraction of the advertising budgets of the participating tobacco firms or as a sincere effort to discover any harmful effects of tobacco smoke.

Dr. Little and spokesmen for the innocence of tobacco have repeatedly denied proof of a causal relationship between smoking and lung cancer. They can demand "proof" with impunity, for overwhelming evidence can fall short of mathematical proof. However, public health measures are usually based on overwhelming evidence.

Dr. Rutstein's letter (p. 46) was dispassionate—his questions concise and direct. Dr. Little announced that he would reply "constructively." In his statement (p. 49) he did not refer to either Dr. Rutstein or any of his specific questions. He essentially restated his reply of July 1957 to the Surgeon General's statement (p. 44), and referred to contrary opinions of "a number of distinguished statisticians," naming only Berkson who had shown that it would have been *theoretically* possible for the findings of *one* (Hammond and Horn, 1954) of the many statistical studies to have resulted from sampling bias. Four statisticians have pointed out the weaknesses of Berkson's arguments.

Knowledge of the relationships of cigarette smoking to lung cancer has gone far beyond the statistical association and the demonstration of carcinogenicity for animals. Much of the pathogenesis of lung cancer has been worked out. Some of it has been reviewed by the Study Group on Smoking and Health (p. 57). In other areas of research epidemiologic, experimental, and pathogenetic methods all play a role in studying the causes of human disease. One gets the impression that they are unacceptable here. It would be interesting to know, as a starting point, what Dr. Little does accept of this evidence which "claims" to establish a relationship. It would help, too, if he would state precisely what kind of information he requires before he will be satisfied that smoking is a major cause of lung cancer.

The credulous public tends not to distinguish between expert opinions and opinions of experts outside their own specialties. Many do not even distinguish between fact and opinion. Have the tobacco interests and the public press capitalized on these facts by making the issue "controversial"?

The challenge to the tobacco industry is not how courageously it can fight accumulating evidence, but how bold and imaginative it can be in helping to solve the most serious problem it has ever faced and one of the most serious problems in public health today. An early solution could be found through cooperation between industry and independent medical research.

Dean F. Davies, M.D., Ph.D.
ACS Administrator for Research on Lung Cancer.

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Lung Cancer Research . . .

A Workshop Conference on Lung Cancer Research was held in Virginia Beach, Va. on November 7 and 8, 1957, sponsored by the American Cancer Society through its lung-cancer research program. The Chairman of the Conference was Dr. David A. Wood, past president of the Society, who opened the meeting with a welcoming address. The participants then separated into seven workshops according to their aptitudes and experience. There were approximately 10 to 15 investigators in each workshop including a leader and a reporter. The discussion areas were:

Workshop I—Chemistry of Tobacco Products and Air Pollutants
Workshop II—Biologic Testing
Workshop III—Histopathology
Workshop IV—Biologic and Chemical Mechanisms
Workshop V—Radiation and Occupational Hazards
Workshop VI — Physiological and Psychological Factors
Workshop VII—Cytology

The workshops met in the morning and afternoon of the first day and the morning of the second day. In a joint session in the afternoon of the second day, the reporters presented highlights from the workshop to which they were assigned. These summaries are being made available to the participants and a limited group of other interested scientists.

Many favorable comments were received at the Society's headquarters regarding the effectiveness of the Conference and investigators have reported that their research has already been modified, improved, or expanded on the basis of the exchange they had with other participants.

Cancer Symposium in May . . .

The Physicians' Symposium on Cancer sponsored by the Knox County (Tenn.) Unit of the American Cancer Society will be held at the C'est Bon Restaurant on the Alcoa Highway, Knoxville on May 22, 1958. Participants include: Captain William M. Silliphant, MC, USN, Director, Armed Forces Institute of Pathology: *Carcinoma in Situ of the Cervix Uteri;* Dr. Juan A. del Regato, Director, Penrose Cancer Hospital, Colorado Springs: *The Fundamentals of Radiotherapy of Cancer;* Dr. John deJ. Pemberton, Professor (Emeritus) of Surgery, Mayo Foundation: *Some Aspects of Carcinoma of the Thyroid Gland;* Dr. G. H. Klinck, Chief, Endocrine Pathology Section, Armed Forces Institute of Pathology: *The Pathology of Thyroid Cancer;* Dr. G. A. Andrews, Chief, Clinical Services, Oak Ridge Institute of Nuclear Studies, Oak Ridge: *Radioiodine in the Study and Treatment of Cancer of the Thyroid.* All five speakers will also participate in a panel discussion on thyroid cancer. Physicians and medical students are cordially invited.

> Starting from the premise that tobacco contains a terrible poison, of which I have just spoken, smoking should in no circumstance be permitted, and I venture to hope, so to say, that this my lecture 'On the Harmfulness of Tobacco' will be of some profit to you. I have finished. *Dixi et animam levavi!*
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> —Anton Chekhov: The Harmfulness of Tobacco, 1886.

quency among women with endometrial cancer (Sommers, Boston U.) . . . Thyroxine lowered the sarcomagenic action of dibenzanthracene in mice, and thiouracil increased it (Pelner, Swedish Hospital, Brooklyn, quoting Bather and Franks) . . . Otherwise resistant rats, when placed on an iodine-deficient diet, developed goiters and breast cancers, or, if they escaped this fate, they bred late, if at all, couldn't nurse their young, and often killed them (Dunning, Miami U.).

Epidemiology: Various surveys by Spencer, Stocks, Legon, and the World Health Organization indicate that the cancer incidence is high in goiter belts of the world and of various countries and low where iodine is abundant in foods.

Thyroid Treatment: Loeser (England) has reported that of 16 breast cancer cases (12 with axillary metastases) maintained with thyroid for four or more years following mastectomy, only one had shown recurrence. He contended, on the basis of these and other equally interesting clinical observations, that hypothyroidism promotes cancer development and growth in humans and that hyperthyroidism suppresses them . . . Lemon (Boston U.) found that cortisone plus thyroid helped about 65 per cent of advanced breast cancer cases, about the same effect as adrenalectomy or hypophysectomy.

Environment and the Thyroid: Diet may depress thyroid function. Greer (U. of Oregon) has listed as having marked effect such foods as rutabaga, turnip, peach, pear, strawberries, spinach, and carrot, and as having moderate effect grape, celery, green pepper, orange, apricot, peanut, pea, string bean, walnut, filbert, honeydew, cabbage, lettuce, beet, oyster, milk, liver, clam, and grapefruit. He emphasizes however that goitrin (the active principle liberated by enzymic action from progoitrin) has been isolated only from turnip and rutabaga . . . McGavack (New York) has charted as contributants to multinodular goiter emotions, physiologic epochs, excessive physical stress, imbalances of the autonomic nervous system and endocrine glands, an iodine deficiency or excess halogens, and such drugs as antithyroid compounds, thiocyanates, sulfonamides, thiocarbonamides, aureomycin, and penicillin . . . Bongiovanni (U. of Pa.) has reported a rise in neonatal goiter due to drugs and food fads during pregnancy. (Man at Yale has adduced evidence that both thyroid hormone and thyroid-blocking agents penetrate the placenta) . . . Van Middles-

worth (U. of Tenn.) and others have measured I^{131} in Middle West cow thyroids and estimated it in milk following atom bomb blasts in Siberia and the Pacific . . . Cohn has shown that forced feeding depresses rat thyroid activity . . . Several groups (Samuels, Ackerman, and others) have given direct or indirect evidence that thyroid function may fall off in middle age.

Random Observations: Anti-diabetic sulfonamides induce hypokalemia, edema, anemia, asthenia, weight increase, and BMR variations (Villaverde) . . . Tumor-bearing mice and hamsters concentrate radioactive sulfonamides less in spleen, liver, kidneys, and blood than non-tumorous animals (Argus) . . . Cancers, even early ones, depress glucose metabolism (Gellhorn) . . . Tumor-bearing rats increase oxygen consumption and energy expenditure with a smaller increase in CO_2 (Pratt) . . . 64 per cent of hypothyroid rats took a mouse sarcoma as compared with 13 per cent of euthyroid litter control mates; and tri-iodothyronine depressed the takes (Schatten) . . . Carcinogens inhibit body growth (Landauer, Gutman) . . . Serotonin, which stimulates involuntary muscle and raises blood pressure and body temperature, is 1,000 times as potent as histamine in inducing anaphylaxis . . . Some spontaneous remissions of cancer follow prolonged high fever . . . Thyroid hormone has dramatic effect against some of the commonest diseases, the rates of which are rising rapidly, including mental conditions (Morton, Danziger, and many others) and alcoholism (Rawson, Koch). Thyroid depression of blood cholesterol levels is well known.

The role of thyroid hormone in enzyme aspects of cancer is poorly understood -- perhaps because it has been studied very little. Potter (U. of Wis.) reports finding transhydrogenase absent or present only to a negligible extent in Novikoff hepatoma. Emmelot and Brombacher reported finding that thyroxine uncoupled oxidative phosphorylation in some tumor mitochondria but not in others. One cannot say with complete assurance at this time that the thyroid would be involved in catalase, succinoxidase, and many other enzyme deficiencies now recognized in various tumors. Kochakian has shown depressions of organ alkaline phosphatase, ATPase, and transaminase in hypothyroid animals.

New evidence of the interdependence of various hormones appears to implicate the thyroid in many heretofore seemingly isolated endocrine events.

COMING MEDICAL MEETINGS

Date 1958	Meeting	City
Apr. 11-13	American Association for Cancer Research	Philadelphia
Apr. 13-18	John A. Andrew Clinical Society	Tuskegee Institute (Ala.)
Apr. 13-19	American Society for Experimental Pathology	Philadelphia
Apr. 16-18	American Surgical Association	New York City
Apr. 17-19	American Association of Railway Surgeons	Chicago
Apr. 19-25	Industrial Medical Association	Atlantic City
Apr. 21-23	American College of Obstetricians and Gynecologists	Los Angeles
Apr. 21-26	American Academy of Neurology	Philadelphia
Apr. 24-26	International Society of Internal Medicine	Philadelphia
Apr. 24-26	American Association of Pathologists and Bacteriologists	Cleveland
Apr. 27-May 1	Society of American Bacteriologists	Chicago
Apr. 28-30	Tri-State Hospital Assembly	Chicago
Apr. 28-May 1	American Urological Association	New Orleans
Apr. 28-May 2	American College of Physicians	Atlantic City
May 2-4	Student American Medical Association	Chicago
May 5	American Society for Clinical Investigation	Atlantic City
May 8-9	American Pediatric Society	Atlantic City
May 13-15	Mississippi State Medical Association	Jackson
May 16-18	American Association for Thoracic Surgery	Boston
May 17-18	American Otological Society	San Francisco
May 19-20	American Laryngological Association	San Francisco
May 19-21	American Gynecological Society	Asheville
May 19-23	American Trudeau Society	Philadelphia
May 19-24	National Tuberculosis Association	Philadelphia
May 20-22	New England Postgraduate Assembly	Boston
May 20-24	American College of Cardiology	St. Louis
May 21-23	American Laryngological, Rhinological and Otological Society	San Francisco
May 21-23	American Broncho-Esophagological Association	San Francisco
May 21-23	Middle Atlantic Hospital Assembly	Atlantic City
May 25-31	World Congress of Gastroenterology	Washington, D. C.
May 30-31	American Gastroenterological Association	Washington, D. C.
June 4-8	American Dermatological Association	Sun Valley, Idaho
June 9-13	American Nurses Association	Atlantic City
June 15-21	American Society of Medical Technologists	Milwaukee
June 16-18	American Neurological Association	Atlantic City
June 16-20	Canadian Medical Association	Halifax
June 18-22	American College of Chest Physicians	San Francisco
June 19-20	American Geriatrics Society	San Francisco
June 19-21	The Endocrine Society	San Francisco
June 19-22	American Medical Women's Association	San Francisco
June 21	American Academy of Tuberculosis Physicians	San Francisco
June 22-28	Congress of International Federation of Gynecology and Obstetrics	Montreal
June 23-27	American Medical Association	San Francisco
June 25-July 1	International Congress of Urology	Stockholm
June 29-July 3	American Proctologic Society	Los Angeles
July 6-12	7th International Cancer Congress	London
July 9-10	Rocky Mountain Cancer Conference	Denver

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